Family Medicine
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Family Medicine: Current Concepts and Future Practice

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A young person entering an American medical school today might think that family medicine (FM) has always existed, with courses and clerkships in the predoctoral curriculum, hundreds of postgraduate programs across the country, and the presence of residency trained, board-certified family physicians in the community serving as role models. But that assumption would be wrong.

In its early years, the specialty of family practice had originated within the lifetimes of all its practitioners. Today, that specialty, now called family medicine, is in its fifth decade, and many of today's family physicians (FPs) were born following the pioneering efforts in the late 1960s and early 1970s to establish the discipline we know today. Some currently practicing FPs were in grade school and high school while family physicians struggled to attain clinical credibility, hospital privileges, and curriculum time in medical schools. Some were in practice during those times. All have benefitted from the specialty's success since its beginning in 1969. Not all know the remarkable and inspiring story of the family practice/family medicine movement, and for this reason, we begin this book with an overview of the specialty's origin, evolution, and current status.

One important function of reference books is to serve as historical records of significant milestones for a specialty and the thinking in a discipline during the time of each edition's life. Sometimes, this record shows how much things have changed: In Osler's *Modern Medicine*, published in 1907, Sir William Osler (1849–1919) tells how to treat diabetes mellitus with opium and arsenic, although adding "the writer rarely resorts to them" [1]. Nor do we do so today. And sometimes, a review of past writings reveals beliefs and values that have not changed over the years. Near the end of his career, Osler also wrote: "It is more important to know what patient has a disease, than what disease the patient has" [2]. In fact, in many ways, Osler's thinking about patient care and teaching seems today to have helped set the stage for what would follow a half century later. After all, family medicine is the specialty that emphasizes caring for the patient, not simply making the diagnosis and treating the disease.

A Very Short History of the Specialty

Family practice in the United States of America evolved from general practice, which was the dominant force in health care until the mid-twentieth century. Here is how it happened.

Introducing the Family Practice Approach

Medical care in the United States has been described as characterized by aggressive action, a mechanistic approach, problem orientation, and an emphasis on victory over disease [3]. This connotes that the good physician will record a comprehensive history, perform exhaustive testing, identify and fix the affected organ, and cure the disease. Into this setting came family practice. In contrast to an aggressive assault on disease, family physicians championed *longitudinal health care*, which allowed both patient and physician to understand the natural history of illness and to share decisions over time. A *relationship-based*, *biopsychosocial approach* integrated with the evolving new technology was advocated. The emphasis of

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family practice was on the *broad-based care of the person and family*, rather than a narrow focus on the disease problem. Finally, family physicians advocated *improving the quality of life*, particularly important when patients suffer chronic or terminal illness, and victory over disease is not really possible. These principles, more often intuitively shared than explicitly articulated during the early years, guided subsequent historical events.

The Early Years

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 when the wisdom of experts was challenged. These events coincided with a decline in access to broad-based health care in the United States, which occurred for a number of reasons: too few medical graduates to serve America's growing population, a trend toward specialization that began following World War II, and generalist training that was inadequate for an increasingly complex health-care system. In response, the American public and far-sighted health-care planners decried the fragmentation of American medicine and called for the creation of a physician who specialized in personal health care – the family physician [4, 5].

With the support of the American Academy of General Practice (AAGP) and US general practitioners, in 1969 family practice became the 20th American medical specialty.

Four early decisions helped shape the future of the new specialty. A *specialty certifying board* – the American Board of Family Practice (ABFP) – was created in 1969; until 1979, a physician could qualify to sit for the certifying examination based on practice eligibility, but since then all candidates for specialty certification must be graduates of approved 3-year family medicine residency programs. *Three-year residency training programs* were established, in contrast to the prior norm for general practitioners of a single year of internship perhaps supplemented by a 2-year general practice residency. *Mandatory recertification* was pioneered by the ABFP, and all US board-certified family physicians must take a periodic recertification examination; most other specialties have since followed this lead in various iterations. Finally, *mandatory continuing medical education* was required by both the American Academy of Family Physicians (AAFP) and the American Board of Family Practice. The latter organization, now the American Board of Family Medicine (ABFM), requires 300 h of approved continuing medical education every 6 years as one component of the recertification process.

The new specialty began with 15 residency training programs, most converted from previous 2-year general practice training programs. Federal grant programs supported new departments of family practice in medical schools, and clinical departments of family practice were formed in community hospitals across America. From 1969 until today, the family practice/family medicine movement has continued to gain momentum, with solid gains in student interest, 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 in the United States

There are more than 800,000 practicing physicians in the United States; less than one third of these are primary care physicians. Of this number, 90,000 are family physicians, and 12,000 are general practitioners [6]. Today, there are 461 US family medicine residency training programs in community hospitals and academic medical centers. In the early years, a few medical schools created departments of family medicine, often prompted by state legislative mandate or the prospect of federal grants; today, almost all US medical schools have departments of family medicine or other academic family medicine units.

In the beginning, family practice entered the academic setting as both a new specialty and a social movement, aiming to refocus health care on the patient and family; this perceived intrusion was not always welcomed. A patient seen by a family physician was sometimes perceived as a loss to some other

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specialist. Today, medical education and health-care delivery are profoundly influenced by family medicine values, both through the impact of our presence throughout the health-care system and through the power of our core mission of caring for the patient.

There are family medicine courses and clerkships in the curricula of almost all US medical schools, teaching students family medicine's core values and approach to health care. The clinical clerkships with community-based family physicians are demonstrating the importance of medical education outside the academic setting. Students who a generation ago would have never seen a multigenerational family of patients or cared for a patient with problems in multiple body systems are now learning to provide truly comprehensive health care and are doing so in the offices of practicing family physicians.

In 1987, Pellegrino [7] 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. The present success of family practice is a tribute to the intellectual foresight, astute social perceptions, and political acumen of a small group of dedicated general practitioners." Family conferences, shared decision-making with patients, home care, and community-based research are now respected components of twenty-first-century health care. Family physicians are the only physicians who are distributed across America in the same geographic proportions as the American people. Last year, family physicians enjoyed a five percent gain in income, outstripping inflation [8]. Today, we see the continuation of this story as family physicians assume leadership in national medical organizations, such as the American Medical Association (AMA), hold important roles in determining health policy, and become deans of medical schools in the United States. For further information about the history of family medicine, see chapter "▶ Chronology of the Evolution of Family Medicine as a Specialty in the United States," which provides a chronology of the evolution of family medicine as a specialty in the United States.

Family Medicine and General Practice Around the World

Family medicine has a long history in Canada, as well as in the United States. In countries outside North America, family and general practice has evolved in various ways. In Spain, for example, the Royal Decree of 1978 officially endorsed the specialty of family practice: "The family physician shall constitute the fundamental figure of the health system" [9]. In England, the general practitioner (GP) is the key provider in the National Health Service, and the countries of the European Economic Community (EEC) have agreed that postgraduate training in general practice should be a minimum of two full years, of which 6 months should be in an approved practice. There is a European Academy of Teachers in General Practice and Family Medicine (EURACT) founded in 1992.

Family medicine residency programs exist in a number of Latin American countries. There have been family medicine training programs in Chile since 1982. In Cuba, the family physician is the chief provider in a comprehensive health plan for Cuban citizens. Family practice has played a role in the health care of Mexico since the 1970s.

In 14 Asian Pacific countries, there is a core curriculum in family medicine. Family medicine is well established in South Korea, Malaysia, Singapore, Hong Kong, Taiwan, and the Philippines, as well as in Australia and New Zealand. Japan, Russia, India, and China now have family medicine training programs. In Ukraine, pediatricians and internists have been retrained as family doctors to serve as the lead physicians in their health-care system. The government of Vietnam has declared a commitment to deploy trained family physicians in the 10,000 health centers serving the country's population of 88 million people.

There is family medicine training in South Africa, Egypt, Nigeria, and Lesotho. An Arab Board of Family and Community Medicine includes members from 15 Arab countries.

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The nature of day-by-day practice varies from country to country, and 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.

The international group uniting family medicine and general practice is the World Organization of Family Doctors (WONCA), comprised of 126 member organizations in 102 member countries, with membership of some 300,000 family doctors worldwide. In 2015, Istanbul, Turkey, hosted the 20th WONCA Europe Conference. The WONCA World Conference will be held in Rio de Janeiro, Brazil, in 2016.

Philosophical Tenets and Their Impact on the Practice of Medicine

Key values regarding care of the patient and an innovative approach to medical thinking and health-care delivery are important to family physicians in the early twenty-first century and have influenced the global practice of medicine.

Enduring Values

Family physicians are bonded by shared beliefs. They advocate *continuing care* of the individual and family as crucial to the patient-physician relationship and as an effective process of providing care. This continuity allows FPs to increase their knowledge of the patient at each office visit, reducing the need to have the patient recite past medical history, social history, and so forth over and over at each clinical encounter. *Comprehensive care* is an important tenet of family medicine and involves full-service health care of both sexes and all ages. Because FPs emphasize that the patient should receive appropriate care at the right place and at the right time, they place a high premium on *coordinated care*. This emphasis on coordinated care has made family physicians the ideal primary care clinicians in capitated care settings, sometimes metaphorically serving as "conductor" of an orchestra of limited specialists. Finally, a *family-centered approach* has been a cornerstone of family medicine, with increasing recognition that our concept of family includes such diverse units as single-parent families, collective living groups, and same-sex couples. In a family medicine office, a four-generation family of patients is not uncommon.

Relationship-based health care is the philosophical foundation of the specialty, and understanding personal accountability is the key to understanding family medicine. McWhinney [10] writes: "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." The family physician will also often ask about the patient's children, parents, job, vacation, dog or cat; many physicians tell their patients about their own hobbies, travels, children, and pets, becoming, in a sense, "a member of the family."

Family physicians have a community-based health-care orientation. As individual practitioners, family physicians can profoundly influence the health of a community and can also share their knowledge by serving on the boards of local agencies, such as a volunteer health clinic or adult day care center. In addition, many FPs are leading efforts in population-based health care, extending from care of the illness of the individual to addressing community health problems such as smoking use or teen pregnancy.

Formal recognition of the specialty's values resulted in a name change following a vote of the AAFP Congress of Delegates in 2003. The official ABFM definition of family medicine now 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.
>
> (Source: ABFM, Lexington, Kentucky)

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Advances in Medical Understanding

Over the past three decades, family medicine has advanced medical thought in important ways, answering early skeptics who held that FPs had nothing to bring to the table of medical knowledge. One of these is the use of *comprehensive clinical reasoning*, to include consideration of life events, the family's contribution to disease, and the impact of illness on the family. For example, as FPs, we have all seen how juvenile diabetes can affect a family's dynamics in regard to interpersonal relationships, family decision-making, and the allocation of family resources. When a child with diabetes is sick, everything else in the household is of secondary importance, and eventually, relationships can be severely strained; early intervention by the family physician may avert family problems.

Also, FPs have recognized *how problems of living can influence health*. Patients with stressful lives seldom present stress as a chief complaint. Instead, they tell of fatigue, headache, abdominal pain, or weight change – chief complaints that often represent a "ticket of admission" to health care. Recognition of the underlying cause of symptoms is important because, for example, a patient who has surgery to treat chronic back pain may develop severe headaches as a substitute stress manifestation if underlying life problems have not been identified and addressed.

A third area in which family medicine has advanced medical thinking is by teaching residents the *systems approach to health care*. In general systems theory, there is a hierarchy of natural systems that includes molecules, cells, organs, body systems, person, family, community, nation, world, and so forth. To apply systems theory to medicine, if a person's pancreatic islet cells begin to make insufficient insulin, or if a farmer in Africa contracts acquired immunodeficiency syndrome (AIDS), or if a community suffers an earthquake, all systems in the hierarchy are affected. Although family physicians have special expertise in "person" and "family," they need to consider the impact of disease on all systems, from small particles of matter to the planet we all share [11].

The Development of Family Medicine's Literature Heritage

Family medicine is developing a rich literature heritage. The reports describing our clinical research, practice methods, and advances in medical understanding are being published in a growing number of publications and online. Although I will not attempt to list them all (in fear of offending by omission), there are currently at least six family medicine journals worldwide, two major clinical reference books, four student textbooks, several defining and examining the discipline, and at least four review books for board examinations.

These publications not only are important in presenting the family medicine approach to health care, but also allow the intergenerational transfer of values, methods, and reasoning – the "storytelling" of a specialty.

The Clinical Encounter as the Definable Unit of Family Medicine

When future medical historians ask what was the major contribution of family medicine during its first half century, the answer might be the advances made in the traditional clinical encounter, adapting it to the twenty-first century practice. The family physician's clinical encounter is analogous to the surgeon's surgical procedure, the gastroenterologist's endoscopy, or the radiologist's imaging in that *the clinical encounter is what we do*. Its scope includes the FP's approach to undifferentiated problems, communication techniques, physician behavior, presentation of information to the patient and family, involvement of the patient and family in decisions, and ongoing care in the context of family and community.

The office-based clinical encounter typically includes multiple problems [12]. In fact, a patient with six or eight intersecting health problems is not uncommon. In billing, an encounter may be categorized as ranging from minimal to high complexity. However long or short, the encounter is distinguished by a broad-based and longitudinal approach that is often not seen in care provided in other specialties.

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Over the years, the family physician's clinical encounter has become more streamlined, cost-effective, and (we hope) clinically astute. The improvements have been achieved by the use of enhanced communication techniques, the use of "high-payoff questions," modern diagnostic and therapeutic instruments such as the fiberoptic nasopharyngoscope, advances in decision analysis, and the use of handheld devices and electronic medical records.

In the current millennium, the clinical encounter is rapidly evolving to reflect the current advances in technology, with contact via the World Wide Web and telecommunications expanding our patient care capabilities, as described below.

Challenges to Family Medicine

At this time, the specialty faces several challenges. These include the increasing complexity of primary care practice today, telemedicine and the health-care technology imperative, the growing tendency to consider health care a commodity rather than a professional service, and the need to maintain the pipeline of medical students choosing family medicine as a career.

Coping with the Increasing Complexity of Clinical Practice

Over the past few years, the scope of care provided by all primary care physicians has increased, chiefly because of pressures to provide care for more patients during the working day [13]. Three or four decades ago, the family physician often saw 40 patients a day. At that time, most patients had bronchitis, sprained ankles, earaches, lacerations, vaginitis, back pain, skin rashes, and so forth – problems usually requiring only short office visits. Of course, there would be some complex cases, such the woman with systemic lupus erythematosus and the middle-aged man with amyotrophic lateral sclerosis, who required longer visits, but those were the exceptions. This is no longer the case in the current fee-for-service family medicine model.

Today's office patient, especially if elderly, may have a long list of health problems. The patient is also more likely to be *sick* and to require more time than would be needed to treat an ear infection. Why the change? Today, physicians have learned that health care is most cost-effective when the physician sees only those patients who really need face-to-face care. Many instances of back strain, flu, cystitis, vaginitis, and so forth receive advice through the nurse triage line, and only those who cannot be managed by telephone are given appointments. Also, many persons delay coming to the physician because of work or financial pressures. This, therefore, means that there are very few "easy" visits that allow the physician to catch up if behind on the schedule. Clearly, as reported by Okie, the pressure on physicians in all specialties to work faster and accomplish more has intensified [14].

The complexity of current practice has also been augmented by patients having increased emotional problems and mental diseases, such as hoarding disorder, now included in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), published in 2013. Many of these patient concerns are a direct result of lack of family support and work stress. Physicians are being sought for advice and counseling that used to be offered by family members and/or clergy. Patient expectations for a solution to their problems by the physician are higher than in the past and sometimes are unrealistic. New drugs are approved almost weekly, and disease coding has become even more complex with the implementation of the 10th revision of the *International Statistical Classification of Diseases and Related Health Problems* (ICD-10). Medical practice, in any specialty, is not as simple as it once was.

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Mastering Telemedicine and the Health-Care Technology Imperative

Over the past few decades, we have been dazzled by the technologic advances in medicine and science: bariatric surgery as therapy for diabetes mellitus, individual genomic sequencing, and colorectal cancer screening using a swallowed capsule, and now we have wristwatches that include heart rate monitors and devices that can transmit a patient's electrocardiogram to a smartphone. Portable ultrasound devices threaten to make the stethoscope obsolete.

There are "virtual doctor visits" available online. Although the program is designed "to feel like a real physician visit," it is a computer program and not a live doctor [15]. In 2013, the US Food and Drug Administration approved the use of a telemedicine robot to make hospital bedside visits. This means that a patient in a hospital bed, instead of seeing the physician at the bedside, may encounter a robot with a television screen chug-chugging into the room to inquire how symptoms are today. While the technology may be astounding, and admitting that these innovations may save time and allow remote consultations, they also serve to put machines between patient and physician.

A current challenge arises in the "seduction of the screen." In far too many office visits the physician spends more time looking at the computer screen than at the patient, thus losing important visual cues as the patient describes symptoms and feelings. It seems that the physician's fingers are more likely to tap a keyboard than to palpate or percuss. The physical examination is often short changed as physicians rely too much on the laboratory and on imaging [16].

Resisting the Commercialization of Medicine

Family physicians can take the lead in preventing medicine from being converted to a commodity. Health care is not a hamburger or a toaster oven, although insurance companies, health maintenance organizations (HMOs), and government often seem to act as though it were.

In 1969, one of family practice's initial objectives was to combat the fragmentation of health care [4]. At that time, there were too many specialists and not enough generalists, and the patient with hypertension, joint pain, and a skin rash often needed to see three physicians. With the current presence of family medicine in America, this is no longer the case in most communities. Family physicians provide care for most common entities without consultation or referral. And yet, the clinical encounter is changing.

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, often one to be rationed – using tight schedules, relative value units, incentive payments if the physician orders few tests and lowers cost drugs, and financial penalties for minor coding errors. Even the term *provider* reinforces the "commodity" mentality.

What are family physicians to do? We *must* put the patient first, insist on affording the patient enough time so that we can do a good job, work to eliminate incentive payments that create ethical dilemmas for physicians, fight government efforts to criminalize administrative disagreements, and refuse to accept the demeaning epithet *provider*. We must also look for new models that allow more personalized care and that allow us to be paid for the time spent in fulfilling our advocacy and care coordination roles.

Sustaining Family Medicine as a Desirable Specialty Choice

For the past 5 years for which data are available – 2010 through 2014 – there has been a yearly increase in the number of accredited family medicine residency programs, the number of approved first year residency positions, and the number of total residents in family medicine training programs. In 2014, the fill rate of family medicine residency programs through the National Resident Matching Program (NRMP) was 96 %, with 3,000 students choosing family medicine careers [17]. Is this a trend that will continue over time? Perhaps. The year over year increases are small, but they are increases, nevertheless.

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The recent increase in the number of medical students choosing careers in family medicine will still not be enough to end America's shortage of family physicians. In order to have enough family physicians for every American to be served, America would need an additional 65 family medicine training positions each year over the next 10 years, according to a 2014 report of the AAFP [18].

Current Trends and Future Practice

Tomorrow's health care will be shaped by today's events. In selecting what I believe to be the most significant influences on future practice, I chose from a long list that included the current focus on evidence-based health care, the medical and societal impact of our changing demographics, and some events that are occurring as this page is written. The following are the trends I believe most likely to influence family medicine in the decade to come.

Human Relationships in the Age of Telemedicine

Here, we return to the evolving clinical encounter and information technology. Future practice will include more than lasers, fiber-optics, and diagnostic ultrasound. It also will include patient contact via e-mail or voicemail, health data recorded and sent by cellphone, online decision support systems, cloud storage of clinical information, and online consultation with specialists. Just as the automobile spelled the end of "horse and buggy" travel and the telephone allowed direct communication with the physician and the development of scheduled office practice, the Internet is profoundly changing the practice of medicine.

Today, using asynchronous communication, family physicians communicate with patients by e-mail about their health problems. Sometimes the patient sends an e-mail message at 2 a.m., knowing it will not be answered until the next day; this has saved physicians many early morning telephone calls that were not emergencies. Sometimes the e-mail message is a prelude to an office visit. FPs have the potential to speak with patients by telephone as they simultaneously search the World Wide Web for clinical answers. The Internet, with programs such as Skype, is making the "digital house call" a reality. Personal office visits are needed less often and, when they occur, are longer in duration and offer more value for time spent than in years past. With the Internet as part of comprehensive health care, FPs move one step further in actualizing their role as health advisor and consultant.

All the technology mentioned here is being used by FPs somewhere, and within a decade, these functions will be the state of the art everywhere.

The Aging Population

The growing number of older people in the population is the reward for our success in battling infant diarrhea, accidental injuries, treatable infectious diseases, uncontrolled hypertension, and other causes of early death. According to the once-in-a-decade US Bureau of the Census report in 2010, there are 40.3 million Americans age 65 and older, up from 35 million in the 2000 census. The fastest growing segment of our population is the group aged 85 and older. Of course, these are the people with multiple problems involving various organs and whose health-care costs are the highest of any adult age group.

What is the likely impact on family medicine? Family physicians need to prepare to serve an increasingly older patient panel and must be positioned to compete with others who would claim greater expertise. We must insist upon a family medicine approach, emphasizing continuity of care (there is no reason to change doctors when one turns 65), comprehensive care (the FP can care for a wider range of problems than any other physician), and family-oriented care (why fragment the care of the elderly and make it separate from the rest of the family?).

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Globalization and Global Health Disparities

We see the effect of globalization in the economic marketplace: price and wage differences between countries become a little narrower each year. Goods and jobs are increasingly moving freely across borders, as is information about lifestyle and economic opportunities.

The world has yet to experience the full effect of globalization in health care. We in the United States spend billions of dollars annually for antianxiety medication, while in other countries, children die of infectious diseases for want of a vaccine or an inexpensive antibiotic. At the same time, the acquired immunodeficiency syndrome (AIDS), antibiotic-resistant tuberculosis and gonorrhea, and now the Ebola virus are increasingly problems shared by the global community.

The global disparities in health-care spending are striking. According to the *UC Atlas of Health Care* [19], "Health care spending per head for the top 5 % of world population is nearly 4,500 times spending in the lowest 20 %." The 2014 Ebola epidemic in sub-Saharan West Africa highlighted the meager health-care resources of developing nations in many parts of the world.

Former US surgeon General David Satcher, M.D., Ph.D., a family physician himself, proposes three "prescriptions" to improve health worldwide: supporting public health initiatives; enlisting allies such as computer specialists, economists, and patients; and challenging public health leaders to advocate for all health-care consumers [20].

What about family medicine and family physicians in advantaged countries? Our roles may include controlling unnecessary health-care expenditures in America and other developed countries, serving as physicians in developing countries, and advocating for sick persons whatever their nationality. We should also prepare to live and practice in a world where the so-called third-world diseases may be seen in the office next week.

Economic Policies and Health Care

Health policy is the "wild card" in health-care delivery in any country. How national and state governments dictate eligibility for programs and methods of making health-care payments has a strong influence on how health care is provided. Witness what happens in those countries in which the government controls health-care payments, allows unrestricted access to any physician, and mandates relatively low fees. The result is many office visits for minor problems, long waits, very short visits, and frequent (and often medically unnecessary, at least by US standards) follow-up visits for routine problems. In such a setting, patients report, "Three-hour wait, three-minute visit." It is, curiously, the opposite of the model that has resulted from free-market care in the United States – with increasingly complex problems seen in relatively longer office visits by primary care physicians.

On a national basis, the United States is experiencing the implementation of the Patient Protection and Affordable Care Act of 2010 (the "ACA"), the most impactful overhaul of America's health-care system since the initiation of Medicare and Medicaid in the 1960s. As with any governmental mandate affecting a major segment of the economy, the ACA will profoundly affect how health care is delivered in America, depending on a state's decisions regarding funding, how access is controlled, and how clinicians are paid. One clue that common sense and fairness might prevail is the federal policy edict that, beginning January 2015, physicians who manage care for patients with two or more chronic conditions – such as diabetes, heart disease, or depression – will be paid monthly fees for chronic care management services. Such a policy innovation can only be good news for family physicians.

Specific Initiatives and Events Likely to Shape the Future

Sometimes tomorrow is shaped by carefully laid plans; sometimes what happens occurs because "its time has come." The following are two planned initiatives and one apparent groundswell sure to influence how family physicians practice tomorrow.

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- ***Family Medicine for America's Health***. In 2001, the seven major national family medicine organizations launched the *Future of Family Medicine* (FFM) project to prepare the specialty to cope with a rapidly changing health-care environment. One result of the FFM 2004 report was the eventual change of the specialty's name from "family practice" to "family medicine." The report also called for a new, innovative model of health-care delivery: the patient-centered medical home (PCMH). Now, *Family Medicine for America's Health*, initiated in 2013 by the leading family medicine organizations, aims to find ways to improve health outcomes, enhance the patient experience, reduce health disparities, and lower health-care costs, while spreading the message using an ambitious communication strategy titled *Health is Primary* [21].
- ***Four-year family medicine training programs***. Since 1969, the model for family medicine training has been the 3-year residency program. But educators and residents alike have often remarked that the curriculum is tightly packed and 3 years does not seem long enough to master the full scope of practice. Following approval by the Accreditation Council for Graduate Medical Education (ACGME), 2013 saw the initiation of the *Family Medicine Length of Training Pilot* initiative, to be concluded in June 2019. Of the residency programs that applied, 12 were selected and were matched with an equal number of programs to serve as a control group. The extra year of residency training will allow the use of innovative teaching methods, perhaps leadership training, and certainly increased skills in implementing the PCMH [22].
- ***Direct primary care (DPC)***. At the 2014 National Conference of Family Medicine Residents held in Kansas City, Missouri, resident delegates called on the AAFP to "explore the establishment of curricular experiences in the direct primary care practice setting for residents and medical students." They also called for the Academy "to investigate the establishment of residency programs sponsored by DPC practices that would be self-funded, thus providing an option to increase available residency positions that would not require federal legislation." Sponsors of the resolution pointed out the differences between concierge medicine and DPC, explaining that the latter is less costly to patients and "often helps people who are uninsured" [23].

According to the AAFP web site [24], DPC "gives family physicians a meaningful alternative to fee-for-service insurance billing, typically by charging patients a monthly, quarterly, or annual fee (i.e., a *retainer*) that covers all or most primary care services including clinical, laboratory, and consultative services, and care coordination and comprehensive care management." In contrast, in concierge care "the patient typically pays a high retainer fee in addition to insurance premiums and other plan obligations (e.g., copays, out-of-pocket expenditures), and the practice continues to bill the patient's insurance carrier. [24]" Direct primary care offers an option for the family physician to practice medicine as it used to be, free of involvement with insurance companies and the government. DPC physicians tell of small patient panels and 45-min patient care visits, allowing same-day urgent visits, and supplemented by online or telephone contact to address issues that do not need "face time" with the physician. It may well prove to be the preferred model of family medicine health-care delivery in the future and may remove one of the obstacles to students choosing careers as family physicians.

Caring for America and the World

Family medicine has been such a positive influence on health care worldwide that we 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 2010, there were more than one billion visits to non-federally employed, office-based physicians in the United States [25]. During that year, more than

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212 million or 21.2 % of all office visits to US physicians occurred in the offices of family and general physicians [26].

Family medicine has done much more than survive; it has prospered and has had a powerful impact on health-care delivery and medical education worldwide. It 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 role. The values of the specialty put 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. In the twenty-first century, family physicians continue to care for the world. 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
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Human Development and Aging

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General Principles

In committing to caring for the entire family and community, physicians need to have a solid understanding of the range of what is considered normal for each stage of life. Physical, psychological, and social characteristics vary in moderately predictable ways throughout the life span. Understanding what is normal for each life stage enables the physician to identify and treat disease in individual patients, as well as enabling the physician to reassure and counsel patients as they struggle to adapt to normal changes in each stage of life.

The birth of a baby, the death of a parent, or the process of retirement can all precipitate a wide range of physical symptoms. The physician who can put these symptoms into context and recognize the developmental stress which is driving their physical issues can bring much peace and clarity to the patient and their family. In fact, "anticipatory guidance" regarding upcoming stages of development is a central task of "well visits" at every stage of life. This chapter focuses on stages of human development and how they impact upon primary care of the patient.

Stages of Life

While individual human beings vary greatly in their physical, psychological, and social development, there are similarities of direction and timing of development in all three areas. In 1950, Eric Erikson, a student of Marie Freud, developed a theory of the stages of development [1]. Since that time, it has become common understanding to approach human development as a continuum across an entire life span, rather than a process which is complete with the attainment of adulthood.

Prenatal: Embryonic Stage

The earliest stage of human development begins with conception and concludes with the formation of a recognizable human anatomy around 8 weeks after conception. This stage, although only about 2 months long, is responsible for the most dramatic changes visible at any stage of human development. Starting with a single cell, and progressing through multiple cell divisions, differentiation, and development, during this time the heart, brain, spinal cord, limbs, eyes, and ears are all formed. The central task of the embryonic stage is the formation of anatomical structures within the developing human [2].

Physician's Role

Nutrient availability and toxin exposure at the embryonic stage can have dramatic and lifelong consequences. Although many spontaneous abortions are caused by chromosomal errors, early toxin exposure can cause both miscarriage and birth defects. The physician can help to minimize these risks by discussing

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Table 1 Supporting early development

Prenatal	
Maintain	Avoid
Prenatal vitamins/folic acid	Tobacco, drugs, alcohol
Balanced nutrition	Medication exposures
Oxygen levels	X-rays/radiation
	TORCH illness exposures (Toxoplasma, Syphilis, Varicella, Parvovirus B19, Rubella, CMV, HSV)
Infancy and toddlerhood	
Support and troubleshoot breastfeeding	
Track normal and identify abnormal growth patterns	
Educate parents regarding: safe sleep, transportation, toys, baby bottle mouth	
Ensure appropriate supplementation of vitamin D and fluoride	
Identify and refer for developmental delays	
Counsel parents on age-appropriate behavior, discipline and expectations	
Childhood	
Track normal and identify abnormal growth patterns	
Educate parents regarding: home safety, importance of language and reading, nutrition	
Identify and refer suspected developmental delays, learning disabilities, psychiatric issues	
Counsel regarding obesity risk factors	
Support appropriate dental care	
Adolescence	
Educate adolescent and parents regarding puberty and physical changes	
Negotiate and maintain confidentiality	
Identify and treat obesity and eating disorders	
Counsel against drugs, tobacco, alcohol	
Counsel regarding STI's, birth control and pregnancy	
Identify and address depression and other psychiatric issues	

them with prospective mothers during preconception or early prenatal visits. Especially important topics to cover include the importance of avoiding alcohol, drugs, medications with risks for teratogenicity, X-ray or other radiation, and exposure to teratogenic illnesses such as rubella, toxoplasmosis, CMV, and others.

Folic acid is especially important in the normal formation and closure of the brain and spinal cord. For optimal development, the mother needs to consume adequate folic acid for at least the 3 months immediately prior to conception, through the first 3 months of pregnancy. The physician will advise a daily intake of at least 400 IU of folic acid for all women of childbearing age and in particular those who express a desire for pregnancy in the near future. This intervention can significantly decrease the developing embryo's risk for neural tube defects including spina bifida and anencephaly (Table 1).

Prenatal: Fetal Stage

The Fetal Stage begins where the Embryonic Stage left off, with the basic anatomy formed and the fetus approximately 3 cm in size. During the remainder of the pregnancy, the tissues and organs

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continue to differentiate and develop, while growth accelerates. The adequacy of the oxygen and nutrients supplied to the fetus through the placenta will affect fetal growth and development throughout this period.

Toward the end of the Fetal Stage, the fetal anatomy becomes increasingly prepared for the transition to life outside the uterus. Lung development matures toward a point after which breathing air will be possible, and tissues in the vasculature ready themselves to recognize and react to the changes which come with birth, most especially the transition to the lungs (instead of the umbilical cord) as the new source of oxygenation for the body. The central task of the fetal stage is growth and organ maturation toward the goal of function outside the uterus [2].

Physician's Role

In order to support fetal growth and maturation, the delivery of adequate oxygen and nutrients is essential. The physician can best support the developing fetus by helping the mother to address problems which can interfere with the delivery of oxygen and nutrients through the placenta. The physician will screen for and treat hypertension, support the mother's efforts at tobacco cessation, and warn against use of cocaine or other vasoconstrictors, all of which can impair placental function. The physician will also keep an eye on fetal growth through ultrasound and fundal height measurements, in order to identify unexpected problems with growth.

Adequate nutrition will include daily prenatal vitamins, as well as intake of adequate and healthy carbohydrates, proteins, and fats to support fetal growth. During the stress of pregnancy, some women will develop gestational diabetes, causing high rates of fetal growth. The physician will screen for maternal development of gestational diabetes and facilitate careful glucose management to minimize the dangers of birth trauma related to macrosomia.

Finally, the physician will help to manage risks resulting from the coming transition from intrauterine life to birth. Medications such as NSAIDs which can inappropriately hasten the closure of the ductus arteriosus should be absolutely avoided during the third trimester. Medications to which the fetus has exposure in utero will dictate particular withdrawal risks to watch for in the immediate postpartum period, including antidepressants, narcotics, and other drugs (Table 1).

Infancy and Toddler Stages

Infancy begins with birth and transitions to toddlerhood at around 12 months of age. While the mother's anatomy has changed most dramatically with the pregnancy, it is important to remember that birth itself begins an even more dramatic and challenging set of changes for the new family. Parents can become bewildered at finding their way through breastfeeding challenges, sleep cycles, car seat, crib and stroller choices, safety and management. During this period, infants learn to trust that food and care will be available when needed.

Breastfeeding is the earliest developmental challenge for the newborn infant and new mother, and successful breastfeeding is correlated with an impressive number of health benefits for both baby and mother [3].

Sleep is a challenge for both infants and their families: when parents suffer from sleep deprivation related to nighttime parenting of infants, the whole family suffers. The fear of SIDS (sudden infant death syndrome) may further disturb parents' sleep. Putting infants to sleep in the supine position, breastfeeding, and eliminating tobacco smoke from the home can all help to minimize SIDS risk [4]. Some authors advocate a systematic program to train infants (usually older than 6 months) to self-soothe and to regulate sleep on their own [5]. Other authors advocate cosleeping and the family bed [6],

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which is controversial in the literature and correlated with an increased risk in infant deaths. Parents can find this literature confusing and challenging to navigate.

Infants double their birth weight by 4–5 months and triple it by 12 months. They develop the ability to sit and to roll by 6 months; by 12 months, toddlers can pull up to a standing position, and they walk by 18 months. Babies begin to smile and follow faces as early as 2 months. Language skills begin with cooing at 2 months; by 9 months, infants understand the word "No," and by 12 months, they begin to have a few words of their own. Over the next year, toddlers build vocabulary, eventually speaking in 2–4-word sentences. "Stranger anxiety" often sets in around 9 months. By 12 months, infants can find hidden things easily and can follow simple directions. Over the next year, toddlers are increasingly independent, sometimes developing temper tantrums and defiance [7].

Physician's Role

Since successful breastfeeding can have a huge impact on an infant's lifelong health, the physician should begin to educate and encourage expectant mothers to breastfeed long before birth. Encouraging new mothers to learn about breastfeeding through classes, reading, and support from experienced breastfeeding mothers is crucial. The physician should be ready to troubleshoot breastfeeding problems, treat both mother and baby for infections (like thrush or mastitis), and be comfortable choosing lactation-safe medications when the mother requires treatment [3].

Physicians should be comfortable advising new parents on safe sleep practices and identifying potential dangers to the infant: soft bedding, tobacco smoke in the home, bottle-feeding in bed, bed-sharing, especially with parents under the influence of alcohol or drugs [4].

Because deviation from a standard developmental pattern can often be the first clue that the infant has some kind of pathology, the physician needs to understand the range of normal development and to be ready to identify infants who fall outside the realm of normal. It is important to have a clear plan for referral for infants and toddlers who are at risk for developmental concerns, so that parents can easily and appropriately arrange for evaluation, ideally within the home environment. When identified early, and treated with early interventions, developmental disorders can have much improved long-term outcomes [7].

Parents will ask their physician for advice on how to manage difficult family situations such as temper tantrums and defiance. Physicians should be ready to advise parents on the importance of finding a balance between the child's need for independence and the family's need for civilized behavior. Parents should strive to define a few clear rules and be very consistent in their enforcement. It is essential that all parents and caregivers be in agreement and consistent about discipline (Table 1).

Childhood Stage

Throughout childhood, children progressively grow physically, as well as developing skills in the motor, language, social, and cognitive domains.

When supplied with optimal nutrients and a well-balanced diet, children will grow progressively along the expected growth curves for their family and genetic makeup.

Children progressively refine gross and fine motor coordination over the years. They progress from walking to running, throwing, catching, and kicking balls. Athletic participation encourages healthy exercise, maintenance of healthy weight, and development of gross motor coordination. Even the littlest children are able to pick up small objects, and over the years, they develop facility in fine motor coordination: turning pages, printing and handwriting, coloring, manipulating scissors, etc. [7]. In general (although there are, of course, many exceptions), boys develop gross motor skills more quickly while girls

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excel at fine motor skills at younger ages. Academic success often depends heavily on fine motor skills, giving girls an advantage at younger ages.

Language development progresses throughout childhood, building vocabulary and then developing reading and writing skills as well. This language development depends heavily on the language environment of the child from the very earliest ages. Studies show that young children's exposure to spoken words from caregivers varies greatly, and future IQ and educational attainment is highly correlated with the number of words to which a child is exposed [8].

Social skills develop throughout childhood as children learn to manage their own emotions, interact with peers and authorities, and participate in the community. Parents can be very helpful to their children as they learn to navigate social situations gracefully. Often behavioral and developmental disorders such as attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders are most evident in their impacts on the social domain [7].

Cognitively, children are supported in their development both at school and at home. Data concerning the effectiveness of early childhood education programs in improving lifelong cognitive achievement are convincing enough that federal, state, and local governments work to support these programs and make them available, especially to disadvantaged children [8].

Physician's Role

The physician will track a child's growth and work to identify health problems which may be interfering with this growth. Screening for developmental disabilities as well as learning disabilities is a crucial role for the primary care provider. It is important to have reliable connections with developmental screening services and educational and psychological evaluators, in order to connect parents with the appropriate agency when a child is showing signs of needing help. Often the school system will offer the best resources for learning disability testing and treatment. When ADHD is diagnosed, the physician will support the family in developing behavioral learning techniques, as well as by prescribing and monitoring appropriate medications.

Physicians can also support children's language and cognitive development by educating parents about the importance of talking with their children, reading to their children, and maintaining a rich linguistic environment for them (Table 1).

Adolescence Stage

Adolescence is a variable period of human development which begins with puberty and ends with the beginning of adulthood. This is a period of dramatic change and upheaval, both physical and emotional. During this period, the individual begins to separate from the family, depending more on peers and developing self-identity as well as a sexual identity.

Over the past 150 years, there have been major changes in the timing of the onset of puberty, resulting in increasingly younger sexual development. While the average age of menarche in the mid-nineteenth century was near 18, now it is between 12 and 13, and breast development is starting earlier and earlier as well [9]. Reasons for these changes in the onset of puberty are matters of controversy: differences in nutrition and exposures to environmental chemicals are common explanations. The physical developments of puberty include growth in height, increase in hair and body odor, and sexual development: breast development and menarche in girls, genital development in boys.

Often as adolescents experience the hormonal shifts of puberty and struggle to define themselves as separate from their family and parents, teens may exhibit more oppositional behavior [10]. It is important

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for parents to understand and expect these changes, while continuing to build on a shared history of trust and affection throughout these years.

Adolescence is the period during which most substance use patterns begin. More than 90 % of all adult smokers started smoking before age 20 [11]. People who start drinking alcohol before the age of 15 are four times more likely to have alcohol dependence at some point in their lives [12]. The teen years are the highest-risk years for initiation of drug use. During adolescence, alcohol and drug use are correlated with criminal activity, motor vehicle accidents, and suicide.

Sexual identity and development is central to the adolescent experience. In the United States, more than half of all adolescents have initiated sexual activity by the time they graduate from high school [13]. Teens who initiate sexual activity earlier are more likely to have multiple partners and thus are at higher risk for sexually transmitted infections (STIs). Other teens struggle with questions of sexual orientation, and find the adolescent years especially difficult, especially when family pressures or bullying are experienced as a result of individual sexual orientation.

Driving is an important rite of passage in most communities in the United States and represents both an adolescent's increased personal independence and increased risks since motor vehicle accidents are the leading cause of death in this age-group [14].

Physician's Role

As with every other stage, the physician will track growth and weight in order to identify emerging problems. Adolescent obesity and eating disorders are important issues for the primary care physician to identify and to advise the adolescent and family in management.

The physician will often support a conversation between the parents and developing adolescent on the process of puberty, the importance of avoiding tobacco, alcohol, and drugs, and the dangers of sexually transmitted infections and pregnancy. It is important to speak to teens with parents, and alone as well, offering confidential advice to adolescents who may be uncomfortable with disclosing substance use or sexual habits to parents.

Physicians are often asked to fill out medical forms to support an application for driver's permits. This is an opportunity to discuss the dangers inherent in driving and the grave dangers of driving while under the influence of drugs or alcohol.

Teens will come to their family doctor for treatment for STIs, as well as for birth control options. Some teens are in communication with their parents regarding these issues. Others are quite anxious that parents not be informed about this. It is important for the physician to be familiar with their state's laws regarding teen's rights to confidential health care without parental consent (Table 1).

Young Adulthood Stage

Eric Erikson saw Young Adulthood as the stage at which the primary focus was on moving away from self-absorption through the development of intimacy [1, 10]. Roughly, this stage corresponds to the 20s and 30s.

During this stage, many young adults initiate life partnerships, get married, have babies, buy homes, and start careers. As culture changes, the nature and length of these life partnerships look different, and career patterns look different as well. Couples are cohabiting and delaying marriage to later ages, while same-sex couples are beginning to take advantage of marriage opportunities. Careers are much less likely to involve lifelong commitment to a single company and much more often will involve a succession of

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different career experiences. The average age at which women give birth to their first child is younger than the average age of first marriage, and in the United States, 40 % of infants are born to unmarried mothers [15].

Young adults' sexual health concerns range from STIs and the avoidance of pregnancy to preconception counseling and infertility.

As young adults settle down into a long-term relationship, they often begin to plan their careers, their relationships, and their health around an upcoming pregnancy. For many couples, the pregnancy and subsequent parenting is a hugely challenging and maturing time, and for others, the experience of infertility can be even more challenging. Because couples blame both themselves and the partner for infertility, relationships can become strained and fragile, while others can become strengthened by the shared pain.

Physical strength and endurance peaks during young adulthood, yet the structured athletics which are available throughout grade school and high school are no longer a part of the young adult's culture. Young adults who successfully make the transition from team sports to individual athletic activity can maintain high levels of fitness throughout the young adult period. Others who have a hard time persevering in workouts outside of the team atmosphere will find themselves gaining weight and losing fitness during this stage.

Physician's Role

Young adults will look to the physician for STI treatment, birth control counseling and methods [16], preconception counseling, preadoption physicals, and infertility counseling. Many family physicians offer prenatal care, and this is a very important opportunity for the care of young adults. In addition, the family physician has a unique ability to support young mothers in the breastfeeding experience and to counsel young parents regarding their children.

Young adult athletes primarily seek care for athletic injuries, and physicians with sports medicine experience can be of great help. Former athletes and others who struggle with obesity will come to the physician for weight loss advice and sometimes a new diagnosis of hypertension (Table 2).

Middle Age

Middle age is somewhat variably defined as the years between 40 and 65. Erikson saw this as a period in which the central developmental focus is on making the world a better place for the younger generations coming after. His terms for the tension inherent in this focus are "generativity vs. stagnation" [1, 10].

Most cognitive attributes peak during the period of middle age [17], while physical strength begins to wane. In most intellectual and managerial professions, the leadership is primarily made of people in their middle ages. Most people expect their careers to peak during these years.

It is also during the years of middle age that people's reports of personal happiness reach their lifelong lows [18]. There is a culturally powerful myth which prescribes a "crisis" to the experience of midlife. Although this is a possible experience of midlife, many more people merely experience a period of relatively lower mood than at other times.

From the point of view of family experiences, the middle years are often a time of stresses, as the person feels pressure to help both their children who are getting started in life, as well as their parents whose health is failing. Colloquially known as "the sandwich generation", this period can be a source of significant distress during the middle years [19, 20].

Physically, there are a number of changes during the middle years. Physical strength and endurance have peaked and are now declining. BMI peaks during the middle years [21]. During the late 40s and early

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50s, most women experience perimenopause and menopause. Their cycles become more disorganized and eventually stop, accompanied by hot flashes and other symptoms. While menopause is a predictable biological change within the entirety of the life cycle, many emotional meanings have come to be attached to these hormonal and physical changes. Some women see these changes as being a sign that their youth, health, and usefulness is over. Others see menopause as an invigorating time when they are set free from vaginal bleeding and contraceptive concerns.

Yet another experience of midlife, "the empty nest" can be experienced as either mournful or invigorating, depending on whether parents have maintained their own relationships, interests, and career aspirations throughout their child-rearing years [19, 20].

Finally, the middle years are the years in which the most prominent chronic illnesses tend to appear in great numbers in the population. Hypertension, diabetes, obesity, and depression are all present in higher numbers in the middle years than in younger age-groups.

Physician's Role

During the middle years, the physician will need to be vigilant in order to identify and treat illnesses as they appear. Ideally, the physician will find ways of motivating their middle-aged patients to commit to lifestyle habits which will minimize their risks for hypertension, diabetes, obesity, and depression, but inevitably some patients will develop these common conditions and will need appropriate and comprehensive care as they develop.

The physician should be ready to talk with women about perimenopausal and menopausal changes and can care for the majority of gynecological, physiological, and psychological issues at this life transition.

Physicians can be of special assistance to middle-aged patients who are struggling to care for both elderly parents and troubled teens. The relationship of trust that the physician has can extend to trusting relationships with other family members. Family physicians can have unique insights into the many pressures on the family and can encourage caregivers to care for themselves as well as their needy relatives (Table 2).

Retirement

Retirement is a relatively new experience in the human life cycle, beginning in the late nineteenth and early twentieth centuries. When Social Security was established in the 1930s, the average life expectancy in the United States was 58 for men and 62 for women [22], while in 2010, overall life expectancy was just under 79 [23]. Since Social Security was originally made for people over 65 in an age when the majority of the population would never reach that age, retirement was originally envisioned as a relatively rare experience. In current times, when life expectancy is most of two decades longer, retirement has become the expectation of the majority of the population.

The retirement years are experienced very differently depending on the health, finances, and life situation of the person [24]. Some people plan ahead financially, retire immediately upon reaching the designated age of Social Security, move to a retirement community, and proceed to participate in the leisure activities available there: golf, crafts, music, etc. Others will continue to play a part in the community in which they spent their working lives: volunteering, serving on boards, helping with grandchildren. Some continue to work part time for an extended period, using the continuing income to add to their financial security or to finance travel or other goals.

Some people find themselves retiring related to their own illness or that of a loved one. For these people, retirement often is a time of heightened involvement in the medical community, and for

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Table 2 Supporting later development

Young adulthood
Contraceptive management
Screening for and treatment of STI's
Pre-conception counseling
Infertility concerns
Sportsmedicine injuries
Prenatal care
Weight management
Middle age
Counseling behavior change regarding diet, exercise, smoking cessation
Identification and treatment of common chronic illnesses: hypertension, diabetes, depression
Counseling and care for menopause and perimenopause
Older adulthood
Screen for common problems: falls, urinary incontinence, osteoporosis
Screen for vision and hearing impairments
Encourage physical exercise
Encourage intellectual activities, screen for dementia
Identify support services as appropriate
Screen for and treat depression
Encourage conversations on advanced directives
Encourage patients to define goals of care, and refer to Hospice when appropriate

caregivers, retirement to care for a spouse or other family member can involve much harder and heavier work than they ever did during their so-called working years.

Because of the structure of health insurance availability in the United States, retirement tends to be a period of relatively better access to health care, due to the Medicare program. Because they have both time and health insurance, sometimes people can be more involved in their own health during these years.

The process of retirement, itself, can be a stressful one, just like any other major life change. It can be difficult for people to develop new activities, friendships, and ways of relating to their spouses after so many years of building habits around their work [25].

Physician's Role

The physician may find that newly retired patients may leave their practice in order to move to a retirement community, or conversely, that established patients may bring in their newly retired parents who have recently moved closer to their children. These new patients will often come with established diagnoses, requiring ongoing care. The physician will need to support the ongoing care needs of these patients, while encouraging them to use their time and resources to pursue healthy exercise and dietary habits.

If new travel destinations are part of the retired person's life goals, the physician will help to make sure that travel immunizations and prophylaxis are followed. Although these vaccines are important for all, it is especially vital to keep up with regular vaccinations against flu and pneumonia for grandparents who are regularly providing care for young children (Table 2).

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Old Age

According to Erikson, the primary tension of the stage of life beginning around 65 and progressing into old age is the tension between ego identity and despair [1, 10]. Many people during this stage in life take stock and become comfortable with who they are and the life they have led. In fact, although depression is certainly an issue for many older adults, reported happiness levels peak during this stage compared with the rest of the life span [18]. During their entire lives, people have been making choices and having experiences, in every case making them more unique and more differentiated from their peers. The older population is considered the most diverse and least homogeneous group of all life stages [25, 26].

During these years, more of the person's friends and family have passed away, and the person becomes more likely to live alone. Because the life expectancy of men is about 7 years less than that of women, and women are likely to be married to men who are older than they, a large part of the elderly population is made up of women, and specifically nonmarried women. Women are more likely to have financial challenges since their lifetime earnings were lower, on average, than were men's [25]. Most people in this age-group have lost family and friends to death, if not a spouse, and will be finding their way through the stages of grief associated with these losses [27].

A number of crucial issues for the quality of life for seniors center around their ability to relate to others and function in the world. Sensory deficits – most especially visual and hearing deficits – can make it very difficult for older people to communicate with others, relate to the world, and stay oriented. Older people who are able to maintain hearing and vision tend to be much more successful in navigating life activities [26].

Physical strength and stamina continue to decrease during these years, as does cognitive function, but for both of these issues, the continued exercise of the skill results in much slower decreases in function. For both physical and mental ability, "use it or lose it" is an important concept, and older people who engage in frequent physical and mental exercise function better overall than peers who do not [17, 26]. Dementias become increasingly common over the older ages and become very frequent over the age of 85. While dementia is considered pathological rather than normal aging, physical and mental activity has been shown to be protective against dementia [17].

Physician's Role

The physician will focus on maximizing function for the aging adult. Screening for difficulty with vision or hearing will allow early detection and treatment of problems which interfere with sensation. Exercise and intellectual activity should be encouraged. Screening for common health problems such as osteoporosis, falls, and urinary incontinence can make a real impact on the lives of seniors. The physician can help the patient and family talk about when is the right time to move to safer housing or to give up driving. Ideally, the physician will have a close working relationship with a social worker who can help to connect seniors with services that are appropriate and specific to their current needs. Overall, the goal will be to maximize function and to minimize pathology over the duration of the older age span.

In addition, the physician will help families to have clear conversations about end-of-life care preferences. Advanced directives allow for patients to designate ahead of time what kinds of care they do and do not desire. When cure is no longer possible, hospice referral and care will allow the patient to continue receiving medical care aimed at quality of life and symptom control. The physician who takes these conversations and referrals seriously can significantly improve their patients' experience of the end of life (Table 2).

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Conclusion

Throughout the span of the human life cycle, from the embryonic stage through the end of old age, the human continues to develop and change. The physician who can keep these developmental stages in mind will be best suited to advise patients as they make the transitions of their lives.

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Stages of Human Development

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Culture, Race, and Ethnicity Issues in Healthcare

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Contents

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The need for cultural awareness and cultural sensitivity has never been greater for family physicians. As access to transportation broadens to more and more corners of the United States and the globe – and as information traverses even more quickly than people – 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 providing 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 mentioned most often, conventionally 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 knowledge, skills, and attitudes learned and passed from one generation to the next. One's identity is ever-changing, shaped by personal experience throughout a person's life. Conclusive statements about culture, therefore, are rarely possible. Cultural norms, on the other hand, are often defined by members of that culture and can be modified over time. One's affinity to his or her culture and its norms can be highly variable, determined in part by the amount of time since his or her family migrated from one society to another, level of education, and socioeconomic status. In fact, there may be more similarities between two individuals of the same socioeconomic status who are from different cultures than between two individuals of the same culture but different socioeconomic status.

Population Demographic Shifts

Demographic shifts in the US population continue at a rapid pace. As a consequence, the Western biomedical model is challenged more than ever before to meet the needs of minority populations who have differing – and sometimes conflicting – views of health and illness.

Census data project an increasingly diverse US population. Between 2010 and 2050, the Hispanic population is expected to grow from 49.7 million to 132.8 million, an increase of 83 million or 167 %. The group's share of the nation's population will almost double, from 16 % in 2010 to 30 % in 2050. The Asian population will grow 213 % or from 14.4 million to 34.4 million. Asians' share of the population will double, from 4.7 % to 7.8 %. The black population will grow from 39.9 million to 56.9 million, an increase of 17 million or 46 %. The black share of the population will remain relatively the same at around 13 %. By contrast, the non-Hispanic white population will increase by only 1 %, from 200.9 million to 203.3 million, a gain of 2.5 million. The non-Hispanic white share of the population will decline from 64.7 % in 2010 to 46.3 % in 2050 [2].

The US population is generally older than it was in generations past. The estimated population median age in 2009 was 36.8, up from 35.3 in 2000 – a natural consequence of 77 million baby boomers who are living longer than previous generations. Altogether, the elderly segment of the population is expected to increase dramatically. A Congressional Research Service report released in 2015 projected that people 65 and older – currently constituting 13 % of the population – would make up 20.2 % of the US population by 2050 [3]. At the same time, the birthrate has remained relatively flat since the 1970s and in 2009 posted the largest 2-year drop in over

30 years, according to the Centers for Disease Control and Prevention [4].

Health Disparities

The United States has experienced great improvements in health, due in large part to advances in medical technology and our healthcare system. Life expectancy increased from just less than 70 years in 1960 to approximately 79 years in 2011, and in general, people live longer, healthier, and more productive lives than before. However, this upward trend is neither as rapid as it should be nor is it uniform across all people in the United States [5].

Life expectancy and other key health outcomes vary greatly by race, sex, socioeconomic status, and geographic location. In the United States, whites have a longer healthy life expectancy than blacks, and women live longer than men. There are also marked regional differences, with much lower life expectancy among both white and black Americans who live in the Southeast [6]. Dr. Martin Luther King summarized this best when he proclaimed at the 1966 Second National Convention of the Medical Committee for Human Rights that "Of all the forms of inequality, injustice in health care is the most shocking and inhumane."

Health Status of African Americans

Health disparities between African Americans and other racial and ethnic populations are striking and apparent in life expectancy, death rates, infant mortality, and other measures of health status and risk conditions and behaviors. Cardiovascular disease is the leading cause of death in the United States, and it is disproportionately more common among African Americans. 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 [7]. The infant mortality rate for non-Hispanic blacks is more than double the rate for non-Hispanic whites. Rates also vary geographically, with higher rates in the South and Midwest than in other parts of the country [8]. In 2010, the prevalence of diabetes among African American adults was nearly twice as large as the prevalence among white adults [5].

Health Status of Hispanics

Health disparities impacting Hispanics are projected to increase as the proportion of Hispanics in the United States grows. 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. The prevalence of obesity among female Mexican American adults during 2007–2010 was larger than the prevalence among female white, non-Hispanic adults during the same period. The prevalence of adult diabetes is higher among Hispanics, non-Hispanic 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].

Health Status of Native Americans

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 less than the percentage screened among white adults [10]. 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 [10].

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 [11]. As a result, chronic hepatitis B associated with liver cancer in APIs is one of the most serious health disparities in the United States.

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 [12]. "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 [13], substance abuse [14, 15], suicide [16], sexually transmitted diseases (STDs) including HIV, and increase incidence of some cancers [12, 17].

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 [12]. 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 [12]. 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 supports are available to the patient.

LGBT Youth

LGBT youth may face unique challenges including rejection from family and friends, bullying at school from classmates and authoritative figures, harassment, and violence [18].

LGBT Elderly

Compared to their younger counterparts, elderly LGBT individuals grew up in an era of

discrimination and less social 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 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 [12]. LGBT elderly who lose their ability to live independently and are subsequently institutionalized may tend to conceal their sexual orientation [12, 19].

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 [20]. STD screening should be offered annually and at shorter intervals for high-risk individuals (e.g., multiple partners, drug use in conjunction with intercourse).

Health Status of Deaf People

Hearing loss is the second most common disability in the United States, accounting for approximately 10 % of Americans [21]. Out of the 8.8 million North Americans who are deaf, it is estimated that between 100,000 and 1 million belong to the Deaf community [22, 23]. Of note, "Deaf" (uppercase "D") refers to the culture and community of Deaf people, whereas "deaf" (lowercase "d") refers to the lack of hearing [23]. 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 [22]. Members of this community were typically deafened during childhood, around age 3, before the acquisition of English language skills [23]. 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 [23]. 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 [21–24]. 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 [25]. 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 [25]. 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 [21]. 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 [25]. In Deaf culture, it would be more appropriate for the physician to first discuss the main medical issue followed by clarifying the treatment plan and moving to

rapport building toward the end [21, 25]. 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 [21]. 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 [23, 24]. 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 [25]. Furthermore, Deaf people are less likely to repeat themselves than non-English-speaking immigrants [23]. 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 [21, 23, 25].

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.

Since 2000, at least 600,000 refugees have resettled in the United States from over 80 different countries, with almost 70,000 refugees in 2014 alone [26]. 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. Although refugees differ greatly in their cultures and countries of origin, patterns of experiences shared among refugees can be observed and may offer some understanding for family physicians seeking to offer care to the refugees and their families.

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 [27].

Medical Screening Examinations

Before being permitted to resettle in the United States, refugees must pass the overseas medical screening exam performed by physicians under the oversight of the Department of State (DOS) and the US Citizenship and Immigration Services (USCIS). The goal of these evaluations is to detect conditions that render a person ineligible for admission (e.g., active tuberculosis or untreated communicable infections) or significant health problems that greatly impair caring for oneself or that might require extensive treatment or possible institutionalization (e.g., pregnancy, inactive

tuberculosis, or other sexually transmitted infections). The initial evaluation should include a full medical history and physical examination. Mental status should be assessed, with particular attention to intelligence, thought, judgment, affect, and behavior. Laboratory evaluation should exclude syphilis and tuberculosis, and appropriate immunizations should be administered [28].

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 [29–31]. In 2014, a Gallup poll revealed that 86 % of Americans believe in God or a universal spirit [32]. 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 [31, 33]. 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 [31]. 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 [31]. 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 [33–35]. Regular spiritual practices have been associated with longer lifespan in some observational studies [35–37]. Over 850 studies have examined the relationship between religious involvement and mental health. Close to 75 % of these studies have demonstrated that religious involvement is associated with the experience of better mental health and coping skills [33]. 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 [34]. 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 Religion and Spirituality in the Clinical Encounter

In the outpatient encounter, an informal spiritual history can be incorporated as part of a social history during an annual physical exam or follow-up visit for new or established patients. Obtaining a formal spiritual assessment can be 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 [35, 38, 39].

Several formal spiritual assessment tools are available to assess a patient's beliefs [31]. One spiritual screening tool suggested by a consensus panel of the American College of Physicians [33, 34] uses four simple questions:

Table 1 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 4th 2015

Table 2 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?"

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?"

The FICA spiritual assessment tool (Table 1) [40] and HOPE spiritual assessment questions (Table 2) [31, 38] use a more comprehensive series of questions to elicit open-ended discussions on spiritual beliefs with patients.

Integrating the Spiritual Assessment with Medical Management

After evaluating a patient's spiritual needs and observances, physicians should document their assessment for future reference or for guiding current treatment. Anandarajah and Hight suggest four outcomes following the spiritual assessment [31]:

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 [35]. Most chaplains are expertly trained in listening and communication skills and have specialized knowledge on how various spiritual paradigms view healthcare [39]. 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 [34].

Approach to the Cross-Cultural Clinical Encounter

Several general guidelines have been developed to guide clinicians during cross-cultural clinical encounters. The LEARN model developed by Berlin and Fowkes [41] 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 and 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" [42]. As a result, this population is less likely to receive preventive care, have regular care, or be satisfied with their care [43], 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 [44, 45].

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 [46]. 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.
7. Test for understanding, especially when nonprofessional 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 [47].

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.

Medical Decision-Maker

In Western culture the decision-maker is typically the patient or next of kin (e.g., spouse, children). However, physicians should be mindful that decision-makers may vary across cultures. For example, a patient may rely on their community or a designated family leader for making important medical decisions. Spiritual and cultural beliefs may influence decisions that result in refusal or delay in medical care. For instance, believers in faith healing may rely on prayer for a miracle and therefore delay medical intervention [35]. Patients of Jehovah's Witness faith tend to refuse both donor and autologous blood transfusions, and if this wish is known, it should be respected whenever possible, even in the setting of a life-threatening emergency. For some patients of Islamic faith, genetic defects are considered God's will [48]; therefore, physicians should facilitate referrals to supportive resources for families that decline genetic screening during prenatal counseling.

Models of Illness and Treatment

Physicians and patients in a cross-cultural encounter may have differing views on what conditions are regarded as "illness" and "treatment." Coining is a practice common in some Southeast Asian cultures that is intended to release unhealthy elements from injured areas and stimulates blood flow and healing. Because this practice results in physical marks on the skin, practitioners may incorrectly conclude that this is a sign of physical abuse.

Staff Gender

Medical care from same-sex health professionals is preferred for some patients. It would be advisable for healthcare providers to announce arrival before entering a room, for example, to give enough time for a Muslim woman to cover her hair and body with a hijab [48]. Some patients may decline sensitive and sometimes even general examinations by opposite-sex physicians for cultural and religious reasons, and care must be taken to respect their wishes. When same-sex providers are unavailable, the patient should be notified and offered alternate suggestions such as having a

female chaperone while a male provider examines a female patient.

Diet

Physicians should keep in mind strict dietary observances such as vegetarian, Kosher and Halal laws, when counseling on nutrition. Some faiths practice fasting, which may affect health status in the chronic or acute setting. For example, in Muslim patients with type 1 or type 2 diabetes who are fasting during Ramadan, care must be taken to counsel on diet, glucose control, and medication management [49].

Human Sexuality

Sexuality outside of marriage, homosexuality, abortion, and birth control may be condemned in several cultures and may result in social ridiculing and shame. Sexual issues may be considered extremely private for some. Discussion of sexually transmitted diseases might be perceived as offensive as it may imply deviation from monogamy [48]. Ensuring privacy for culturally sensitive discussions, counseling and assuring patient confidentiality is of utmost importance.

Mental Illness

Mental illness might be considered taboo in some cultures and religious beliefs. Patients may not acknowledge their mental illness and legitimacy of antidepressants, and therefore a physician should be sensitive to tactful depression screening, building trust, and providing appropriate support.

Death and Grief

Understanding views on death and grief may help navigate the clinician on delivering culturally sensitive end-of-life care and bereavement support. For example, some patients may find comfort in end-of-life prayers and completion of religious rites before death.

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Family Issues in Health Care

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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 individuals' most basic needs for physical and emotional safety, health, and well-being. As such, family members, not health professionals, provide most of the health care for patients. Outside the hospital, health-care professionals give advice and suggestions for the acute and chronic illness, but the actual care is usually provided by the patient (self-care) and family members. Chronic illness requires families to adapt and change roles to provide needed care. The aging of the population and increasing medical technology have led to a significant increase in the prevalence of chronic illness and disability and 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 LGBT couples. The relevant family context may include family members who live a distance from the patient or all the residents of a community home for the developmentally delayed persons. In daily practice, family physicians are most often involved with family members who live in the same household.

Role of the Family in Health and Illness

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. The World Health Organization [2] 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 [3]. 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. 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. Obesity is a major public health problem. 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 partner have better outcomes, especially with long-term follow-up [4]. The family plays an important role in both the development and the treatment of eating disorders such as anorexia nervosa and bulimia [5].

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 [6].

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, 7, 8] were published and used in medical schools and family medicine residencies across the country. The Society of Teachers of Family Medicine sponsored a popular 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.

The widespread adoption of electronic medical records has impacted family-centered care. 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 EMRs have methods for linking the electronic charts of family members, and many don't have ways to easily identify other members of the family or household. Clinicians must often rely primarily on household address to determine family members.

The genogram or family tree has always been a hallmark of family-centered care and a valuable tool but is being used less often. There are no easy methods available for documenting the genogram within most current EMRs. While genogram programs do exist, they are difficult to integrate into the major EHR systems. Instead, family histories are usually recorded linearly in the EMR, rather than graphically, with a list of family members and what diseases they have. Genograms can be created on paper and scanned into the medical record but become difficult to access or modify over time.

Over the past few decades, 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 [9], 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 the 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.

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 heath care reform. We are in the midst of an enormous change in health care as we transition 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 that they achieve, rather than the procedures that 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 get 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 care, better health, and lower costs. The Triple Aim has become the primary goal of health care in the United States. Better care refers to the experience that patients and families have with our health-care system. Patient and family-centered care has become a major focus of most health-care institutions. Medicare now bases a portion of its reimbursement on the scores that were received on patient and family satisfaction. More hospitals and practices are starting patient and family advisory councils to help guide health-care policies. As our health-care system moves 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 to all patients is an important skill. This approach complements

a patient-centered approach in which the physician explores the patient's experience of illness, an experience that occurs in a family or relational context. The patient's presenting complaint can be thought of as an entrance or window into understanding the patient in the context of the family. By exploring the patient's symptoms and illness, 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 or suggesting that the problem is "all in your head."

In a qualitative study of exemplar family physicians, Cole-Kelly and colleagues examined the core components of a family-centered approach with individual patients [10]. 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 exemplars frequently inquired about other family members and were able to keep a storehouse of family details in their minds that they frequently interspersed in the visits. A common time to bring up family details was in the closing of the visit where the physician would punctuate the end of the visit with a greeting to another family member: "be sure to tell John I say hello."

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. 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 "multi-partial alliance" with all family members, rather than triangulating it. 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 and child visits.

Asking some family-centered questions can metaphorically bring the family into the exam room and provide a family context to the presenting problem [11]. 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.

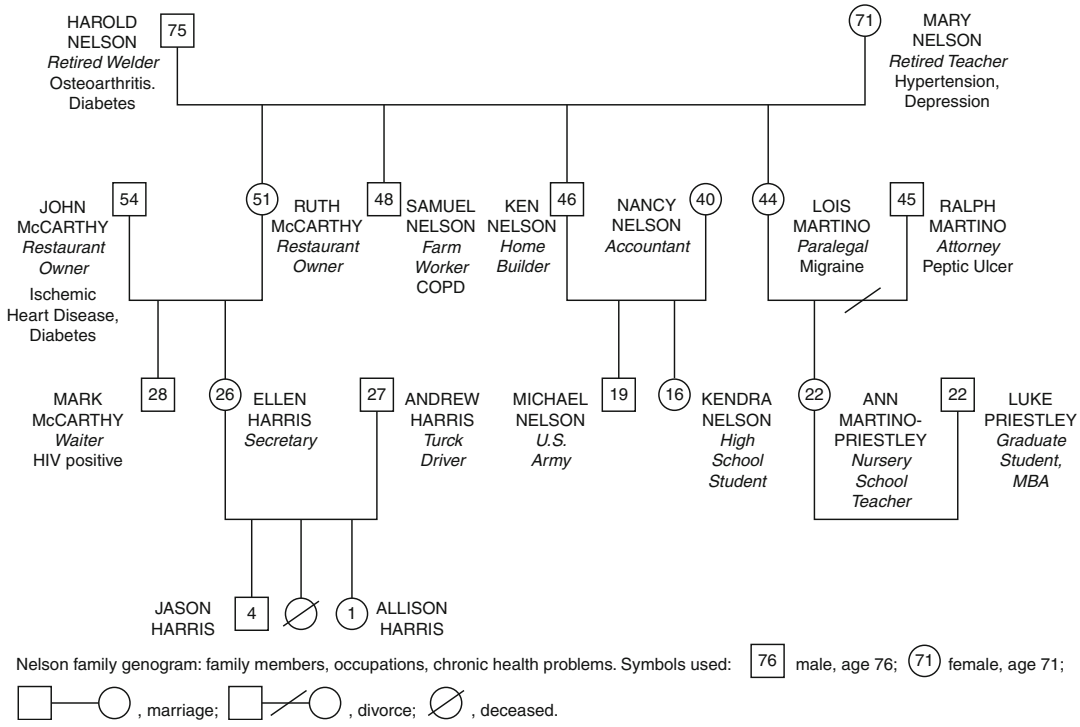

Fig. 1 Genogram

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 [11] (see Fig. 1) and provide a "psychosocial snapshot" of the patient. Genograms provide crucial information about genetic risks and any family history of serious illnesses. With advances in genetic research, detailed genogram should be an essential component of every patient's medical evaluation and database [12, 13]. Ideally a genogram should integrate genetic and psychosocial information.

The genogram can be started at an initial visit and added to during subsequent encounters. It may be quite simple and only include the current household and family history of serious diseases or 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. They are challenging patients, and it is often difficult to obtain family or psychosocial information from them. Since obtaining a family history is

Table 1 Dos and Don'ts of family interviewing

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
Don't let any one person monopolize the conversation
Don't allow family members to speak for each other
Don't offer advice or interpretations early in a family interview
Don't breach patient confidentiality
Don't take sides in a family conflict, unless someone's safety is involved

Source: Adapted from McDaniel et al. [5]

considered a routine part of a medical evaluation, it can often provide access to more relevant psychosocial illnesses. It 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 widely available for most EMRs. Currently, the best option is to create the genogram on paper and scan it into the EMR and use a bookmark or similar system to easily identify its location.

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 [14]. 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, and assisting patients in making decisions. 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 co-parents 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 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 (see Table 1). 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 acting as a traffic cop 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 an initial 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. By making contact with each person, the physician is making clear that everyone is encouraged to participate in the interview.

There are several other important reasons for joining with family members at the beginning of the interview. The physician often has an established relationship with the patient, but may not with other family members. The family member may either feel left out or that his or her role is merely as 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 disrespectful to families and fails to use family members as a resource. It is recommended that the physician greet and shake hands with each family member and find out something about each person. At a minimum, this may be 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.

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 conflict in the family. In these cases, a family member may assume that the physician has taken the side of the patient in the conflict. The physician must take extra steps to join with family members in conflict and establish one's neutrality. The goal in these situations is to develop an alliance with each family member and the patient without taking sides in the conflict. An exception to this goal is when family violence threatens and then safety must be the first priority.

In addition to establishing rapport and building a relationship through verbal communication, 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 that the physician and an individual patient are in a comfortable sitting position and at eye level with one another, so is it 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. 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.

A physician who meets with multiple family members needs to learn how to avoid taking sides with one family member or the exclusion of another. 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, and advances in medical research will continue to have a dramatic impact on family issues in health care. There are increasing demands on families to provide care for 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 will soon 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 family focus or uses a family-oriented approach. Under 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 and their families. A family-oriented approach will become an increasingly valued and effective model in the twenty-first century.

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Family Medicine
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Evidence-Based Family Medicine

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Medicine is built on a foundation of scientific breakthrough, with constant change; a physician practicing for even a few years can appreciate this change. Incorporating the knowledge gained from research into clinical practice, however, is inherently difficult. Historically, it can take many years for medicine to adopt change [1]. This fact is not surprising, as research must be replicated and validated. Yet even validated clinical guidelines can take many years to be widely adopted. The number of clinical trials, clinical summaries, and clinical guidelines produced each year continues to increase [2], and physicians in any specialty can feel overwhelmed with the volume of information. Family physicians who care for the undifferentiated patient can feel that the task of analyzing information in the primary care literature and also multiple specialty areas is insurmountable.

Fortunately, the practice of evidence-based medicine (EBM) does not require physicians to incorporate *all* of the latest research into practice. EBM is defined as the integration of only the best clinical research evidence with clinical expertise and patient values into medical decision making [3]. Physicians who demonstrate knowledge and skills in EBM practice have been shown to have higher quality indicators in clinical practice [4].

The goal of this chapter is to provide practical methods and resources to help family physicians who wish to incorporate EBM into their practice of clinical medicine. The steps to achieve this can be summarized as follows: Ask a precise clinical question, search for the best evidence, appraise the evidence, and then apply the evidence ("Ask, Acquire, Appraise, and Apply").

The first section of this chapter contains foundational information on EBM, including developing a meaningful question, efficiently acquiring evidence, and analyzing the quality of that evidence. The next section outlines the principles of information mastery and synthesized data. The final section reviews application of the evidence through shared decision making.

Foundational Principles of Evidence-Based Medicine

Asking an EBM Question

The methodologies used to apply EBM to clinical practice in a systematic way were not clearly defined until the 1980s. One of the first developments was the crafting of a clear clinical question. A question that seeks to incorporate EBM into practice will contain the following information: a specific population, an intervention or exposure, a comparison intervention, and patient-relevant outcomes [5]. This strategy has been simplified to the mnemonic "PICO" (see Table 1).

Acquiring and Analyzing Evidence

Asking a precise clinical question helps to identify exactly what evidence needs to be acquired. For example, when a healthy teenage patient admits to frequently drinking highly caffeinated energy drinks and wants to know the risks of this practice, the appropriate clinical question is "in healthy teenage patients, do those who drink highly caffeinated energy drinks experience increased health risks compared

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Table 1 Creating a searchable question

	P	I	C	O
Description	**Patient** or **population**	**Interventions** including diagnostic evaluation, treatment, or screening	**Comparison** group	Patient-oriented **outcome**
Example	Healthy adult with upper respiratory infection	Nasal saline irrigation	Usual care	Improvement of symptom scores
Example	Adult female with obesity	Treatment of subclinical hypothyroidism	Monitoring subclinical hypothyroidism	Improvement in weight loss or symptom scores
Example	Adult patient with type 2 diabetes mellitus	Control of systolic blood pressure to <130 mmHg	Control of systolic blood pressure to <140 mmHg	Decrease in stroke rate

to those who do not ?" Then, the necessary information or evidence can be searched for and acquired. Evidence that leads to an answer may exist in the form of individual clinical trials or synthesized data. Because clinical trials are the foundation of research, a review of methods to acquire and analyze individual trials is needed.

Family physicians may find individual trials using an online search engine such as PubMed (http://www.ncbi.nlm.nih.gov/pubmed). PubMed is a database that houses online references to and abstracts for individual trials and synthesized data. It is run by the National Center for Biotechnology Information (NCBI), a division of the National Library of Medicine (NLM) at the National Institutes of Health (NIH). Because PubMed contains multiple databases and links to basic science research, clinicians can find that using the general search function at this resource is cumbersome. Using tools to limit searches to human subjects or the English language may make the process more relevant to the user. The clinical studies search engine will also narrow a search (http://www.ncbi.nlm.nih.gov/pubmed/clinical).

Once a study reference or abstract has been located, it must be evaluated: "Is this piece of evidence helpful?" All types of evidence should be evaluated for relevance, validity, and clinical importance, in that order [6]. If evidence passes all three requirements, then it should be determined whether this evidence supports a possible change to current clinical practice.

Relevance

The first step in evaluating evidence is determining if the question being addressed is relevant to clinical practice. Evidence is most relevant if it describes at least one patient-oriented outcome, is a common issue within clinical practice, and will change clinical practice [7]. Determining relevance can often be achieved by reading the abstract alone.

The majority of evidence published in medical journals is disease-oriented evidence (DOE) [7]. DOE refers to outcomes such as blood pressure, hemoglobin A1C, or DEXA scan results. Although this evidence is vital for understanding disease processes, it may or may not be relevant to clinical practice. In other words, intermediate results that may or may not lead to an improvement in patients' lives should not be studied in depth. Evidence related to changes in patients' lives is patient-oriented evidence (POE) [7]. Results such as morbidity, mortality, symptoms, quality of life, and cost are POE. This differentiation matters, because promising DOE does not always lead to the expected POE; for example, in patients with high cardiovascular risk but no history of MI, supplementation with *n*-3 fatty acids significantly reduces triglyceride levels, but does not decrease cardiac deaths or hospital admissions [8].

In addition to reporting patient-oriented outcomes, relevant evidence should address a common problem within family medicine [6]. Relevant information may differ from physician to physician. Family

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physicians who provide obstetrical care will find a study addressing new developments in managing postpartum hemorrhage relevant, whereas family physicians that do not provide obstetrical care may not.

Lastly, relevant evidence should have the potential to lead to a change in clinical practice [6]. Whether it is a screening test, a diagnostic test, or a treatment option, the intervention must be accessible, affordable, feasible, and sufficiently different than the current standard of care to make a change in practice. Such evidence is referred to as "patient-oriented evidence that matters" (POEM) [7]. Evidence that matters may differ from physician to physician. For example, evidence for the effectiveness of lung cancer screening using CT scans in smokers may not seem relevant to a family physician caring for poorly insured or uninsured patients who cannot afford expensive tests; however, given the scans' ability to identify early and treatable lung cancer, it may be more relevant to physicians who care for populations who can afford this test [9].

Validity and Types of Evidence

Once evidence is found to be relevant to a clinical practice, then the evidence must be evaluated for validity. Validity can be evaluated both internally and externally. For family physicians, external validity usually means that the study population is comparable to a primary care population. Results from studies that include only patients who were referred to a specialty clinic may or may not be similar to results from clinical trials in the primary care population. Studies that exclude patients of certain ages, races, genders, or socioeconomic classifications may also limit external validity.

External validity also includes considering the effect of comorbidities on the evidence. For instance, a study comparing a new pharmacologic treatment of obesity to usual care that excludes diabetic patients will be difficult to apply to the general population because the efficacy and risks of the medication in diabetics are unknown. Even small changes in age or comorbidities can lead to differences in outcomes.

Once evidence passes evaluation for external validity, then internal validity of the study can be explored. Internal validity refers to the level or robustness of the evidence being presented in the study. A good first step is identifying the type of study and the focus of the study. This information should be available in the abstract and often is clearly stated in the title.

All clinical evidence is not equally strong, as illustrated in Fig. 1. Guidelines, systematic reviews, and meta-analyses involve the review and analysis of multiple studies and are often assigned a higher level of evidence than individual trials. Randomized controlled trials (RCTs) examining treatment, prevention, or screening are considered the highest level of evidence for individual trials. This is followed by cohort

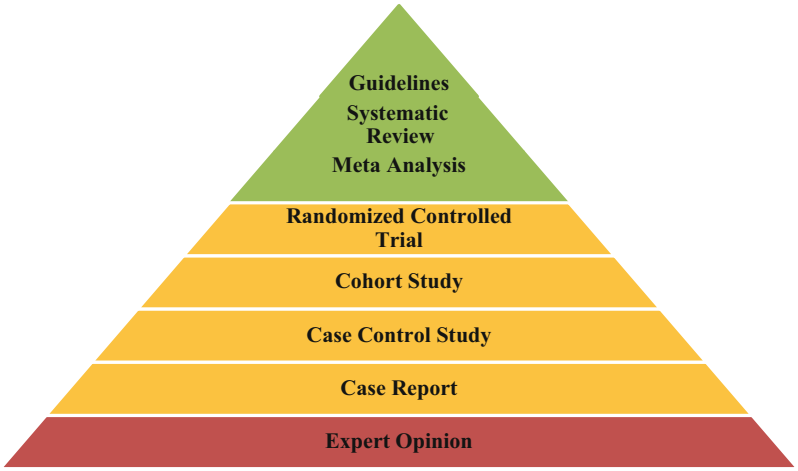

Fig. 1 EBM evidence pyramid

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studies examining diagnosis or prognosis and finally case studies and expert opinion. It is important to note that it is not common for a single scientific trial, no matter how well designed, to change clinical practice on its own; more often, it is the replicability of the results that changes practice over time.

In addition to clinical trials, the medical literature also includes qualitative research. Qualitative research is a tool that physicians use to understand the social, emotional, and experiential phenomena that their patients experience. Understanding and appreciating these forces can help in the implementation of evidence-based care. The goal of qualitative research is to explore complex phenomena that may not be amenable to quantitative research.

Qualitative research is being increasingly valued in the medical literature. Each qualitative study should be evaluated for internal and external validity in the same way that it is done for quantitative studies [10]. Do the people in the study adequately represent the population of patients that the physician is trying to understand? Is the quantity and quality of the information reasonable? Several qualitative studies can also be synthesized, in much the same way that quantitative studies are synthesized [10]. Qualitative information published in the medical literature should not be viewed as competing with quantitative evidence; rather, it should be viewed as a complementary tool for understanding the patient's or medical team's experience. It is also a tool that can help the practicing physician bridge the gap between the quality of care described in quantitative research and the care that is actually delivered in diverse practice communities.

Clinical Applicability

The final step in assessing evidence that is both relevant and valid is determining whether the outcome is clinically important [6]. RCTs aim at altering outcomes, whether it be increasing a benefit or decreasing harm. This change in rate of an outcome is often reported as the "relative risk reduction" (RRR). In general, the RRR can magnify the significance of an intervention by reporting the change as a percent change [6]. For instance, if intervention A drops the rate of Cesarean sections from 10 % to 5 %, the RRR is 50 %. Generally, a more accurate reporting measure is the "absolute risk reduction" (ARR) [6], which reports the change as an absolute change. (For intervention A, the ARR is 5 %, which may not be as clinically important as the 50 % RRR would suggest.)

In practical terms, an even more helpful measure is the number needed to treat (NNT). The NNT is the number of patients who must receive an intervention in order for one positive change to occur. The calculation for NNT is simply 1/ARR. In the example above, the NNT for intervention A is 20. Clinically, this means that for every 20 patients who receive the intervention, one patient will avoid a Cesarean section. The lower the NNT, the more clinically important the intervention.

While evaluating individual clinical trials can be complex, developing a systematic approach makes it easier. Becoming familiar with a few basic study designs and statistical tests provides access directly to the foundational evidence. Physicians should have skill in the evaluation of individual studies, but may find that using synthesized data, which pools the results of individual clinical trials into systematic reviews and clinical guidelines, improves their efficiency.

Information Mastery

The foundational principles of EBM are defining the clinical question and reviewing the evidence in the literature to answer that question. The volume of individual clinical trials published, however, makes evaluation of all clinical trials by busy physicians impractical. The principles of "information mastery" were developed and popularized by Drs. Shaughnessy and Slawson as a means of making the practice of EBM more practical. These principles refine and limit the scope of the EBM information search by

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encouraging physicians to begin their search for information by first focusing on synthesized information when it exists [11].

Information mastery places a high value on synthesized information when it is available. Using synthesized information in the form of evidence-based texts, guidelines, and systematic reviews will reduce the work of searching. Answering clinical questions by searching for relevant and valid information using synthesized information from online resources such as online textbooks, guidelines, and systematic reviews is the key to efficiency.

Data Systems

Physicians frequently access data systems to answer clinical questions. Physicians may use a reference textbook for answering basic questions or clinical questions that are beyond the scope of their usual practice; however, the information published in hardbound textbooks is not easily updated. Frequently updated online clinical resources are easier to access than published hardbound reference textbooks [12]. These resources have Web-based and mobile platforms that can be accessed without a computer; by their nature, they may contain less outdated material. These subscription services can be purchased by individuals or by hospital systems. An evidence-based online resource will include the date of initial publication and the date each topic has been updated; it will also give references to individual clinical trials, clinical guidelines, and systematic reviews. Physicians can answer many clinical questions from an online text or delve further into the reference materials to evaluate those source materials for validity and application. Accessing a systematically updated online text is frequently the most efficient way to quickly answer a clinical question [11].

Clinical Guidelines

If a clinical question is not answered in an accessible online text, then literature review is necessary. Clinical guidelines and systematic reviews are the next sources to search when efficiency is key. Clinical guidelines can be accessed via the Internet at the National Guideline Clearinghouse (http://www.guideline.gov/). Like individual trials, however, each clinical practice guideline (CPG) should be analyzed for relevance, validity, and clinical applicability. Each guideline is only as valid as the process used to develop it. The Institute of Medicine published criteria for analyzing the reliability of CPGs. According to their criteria, each guideline should (1) be based on a systematic review of the existing evidence; (2) be developed by a multidisciplinary panel; (3) consider important patient subgroups; (4) describe transparently the development process to help minimize distortions, biases, and conflicts of interest; (5) provide alternative care options; (6) provide ratings of both the quality of evidence and the strength of the recommendations; and (7) be reconsidered and revised as appropriate [13].

Understanding the level of evidence and the strength of recommendation in a guideline is an important step in analyzing the validity of that guideline. Table 2 lists the commonly used strength of recommendation taxonomy (SORT) that was developed specifically for family medicine [14]. Table 3 lists the level of evidence that is referenced in the SORT criteria. Physicians should be aware that guidelines created

Table 2 Strength of recommendation taxonomy (SORT)

Strength of recommendation	Description
A	Recommendation based on consistent and good-quality patient-oriented evidence
B	Recommendation based on inconsistent or limited-quality patient-oriented evidence
C	Recommendation based on consensus, usual practice, disease-oriented evidence, case series for studies of treatment or screening, and/or opinion

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Table 3 Level of evidence (LOE)

Study quality	Type of evidence		
	Diagnosis	Treatment	Prognosis
Level 1 Good-quality patient-oriented evidence	Validated clinical decision rule Systematic review or meta-analysis of high-quality studies	Systematic review or meta-analysis of randomized controlled trials (RCTs) with consistent findings High-quality individual RCTs	Systematic review or meta-analysis of cohort studies Prospective cohort studies with good follow-up
Level 2 Limited-quality patient-oriented evidence	Decision rules SR of low-quality studies	Systematic review or meta-analysis of low-quality studies Low-quality clinical trials Cohort studies Case–control studies	Systematic review or meta-analysis of lower-quality cohort studies or inconsistent results Retrospective cohort studies Case–control studies Case series
Level 3 Other evidence	Consensus guideline, usual practice, opinion, disease-oriented evidence, extrapolation from bench research		

Summarized from Ref. [15]

from the US Preventive Services Task Force (USPSTF) and other entities use different labeling systems for strength of recommendation and level of evidence.

Systematic Reviews

Disease and clinical summaries are another form of synthesized information that physicians can access when reviewing the medical literature. Clinical reviews can be accessed via the PubMed search engine by limiting search criteria to review articles; however, just like CPGs, not all clinical summaries are equally relevant or valid. Summary articles may be based only on clinical opinion or personal experience. Systematic reviews are a subset of clinical reviews that are based on a review of the medical literature. Many systematic reviews will contain a meta-analysis, which is the use of statistical methods to summarize the results of individual clinical trials [16].

There are several resources that can be used to access systematic reviews. PubMed Health is a search engine that limits searches to systematic reviews; it can be accessed at www.ncbi.nlm.nih.gov/pubmedhealth. Cochrane database is an additional resource for accessing evidence-based systematic reviews; it can be accessed at www.cochrane.org. The Cochrane Library is a complete listing of the systematic reviews of individual topics produced by the Cochrane organization.

Once a systematic review has been located, it must be reviewed for applicability and relevance. Drs. Swanson and Reed listed the following criteria for family physicians to use when evaluating a systematic review: Systematic reviews should be based on a comprehensive literature search including EBM resources such as the Cochrane databases that describe their method of determining which trials to include, have a transparent system for grading evidence, prioritize patient-oriented evidence over disease-oriented evidence, and make an effort to include unpublished or negative data if possible [17].

The concepts of information mastery as described above make the steps involved in answering clinical questions more efficient. Physicians focus on synthesized data that is relevant, valid, and clinically applicable. Once a clinical question has been answered by a review of the evidence, the physician applies this information to clinical care.

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Applying the Evidence: Shared Decision Making

As previously stated, EBM is more than providing evidence-based answers to clinical questions. The final component of EBM is incorporating patient values into evidence-based clinical care. A practical description of implementing EBM in the clinical setting is sharing the best research information with patients and supporting their decision-making processes as they make choices about the care they receive, a process known as shared decision making (SDM).

SDM is more than patient education. It is a process that can be simple or quite complex, but it always involves participation by at least two people – the physician and the patient (or his or her advocate). The process includes communicating information by both parties, building a consensus about the preferred treatment, and agreeing on the care plan to implement [18]. The physician shares prognostic, diagnostic, or treatment information based on the best evidence available. Likewise, the patient shares information about his or her own goals and values. Finally, a plan for care is negotiated and implemented.

For many clinical scenarios, the process of SDM is relatively straightforward. For example, a patient seen in clinic with a urinary tract infection requests and expects treatment to relieve symptoms and prevent complications. A patient wanting to prevent illness might request an influenza vaccination. In each of these cases, both the patient expectation and evidence are clear. The necessary communication includes a review of the risks, benefits, and alternatives of treatment options. This process can be accomplished verbally or with appropriate printed educational materials.

More complex scenarios often occur, requiring more information and support. For example, a patient requesting treatment for an anxiety disorder may want to consider pharmacologic and nonpharmacologic treatment options. A patient with persistent radicular back pain may want to consider surgical, nonsurgical, or complimentary treatment options (such as acupuncture). A patient also may want to have further discussions with family members, caregivers, or friends prior to making a decision on a treatment plan. A recent systematic review of medical decision making showed that physicians typically are open to shared decision making and that patients frequently desire more involvement in this process [19].

Studying the clinical outcomes related to SDM is complex. Physician–patient relationships and communication methods are not amenable to isolated interventions; they vary in location, duration, and complexity. SDM is currently being advocated by the USPSTF based on ethical, interpersonal, and educational considerations [20]. SDM promotes individual autonomy in complex medical systems, enhances communication, and helps promote patient education. A systematic review of SDM demonstrated that a patient report of SDM correlates well with improved patient satisfaction regarding medical treatment with less associated decisional conflict over care decisions [21].

Models for SDM

Several models describe the individual steps involved in shared decision making [22]; a complete description of these models is beyond the scope of this text. It is helpful, however, to approach this interaction systematically. Physicians will need to continually assess patient desire for information and control during this process. A patient's current understanding of a specific medical scenario should be assessed. Information about clinical options should be clearly stated. Risks and benefits of the various care options should be reviewed. Decision support in the form of written material, videos, pamphlets, or online resources may help the patient through the decision-making process. Decision making may progress quickly, or it may take several interactions and include negotiation to reach a decision.

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Barriers to SDM

Physicians and other members of the medical system encounter barriers to adoption of SDM in clinical practice. Currently, there is little financial incentive to promote discussions about healthcare goals. Many physicians have not been educated on techniques to promote SDM. In addition, physicians may feel the time needed to adequately engage in these conversations makes this process unproductive. Finally, studies have shown that both low health literacy and numeracy limit a patient's ability to understand or engage effectively in the decision-making process [23].

Overcoming Barriers to SDM

Physicians can engage members of the healthcare team to facilitate SDM; for example, a clinical pharmacist, nurse, or health educator can help educate patients on many options for clinical care. Hospitals and healthcare systems may also offer classes that promote chronic disease management. When difficult or complex decisions need to be made, physicians can provide patients with decision aids. These tools aid in communication and may help physicians understand what role the patients want to play in the process.

Decision Aids

Decision aids are particularly helpful when there is more than one reasonable option for clinical care. Aids exist in multiple formats: paper tools, videos, and Web-based resources. A valuable decision aid will include disease information and also help patients reflect upon and explore their own values and healthcare goals. Decision aids describe the benefits and potential risks of various treatment options. Some tools have graphic elements that explain difficult concepts such as risk reduction and NNT. These elements help patients consider care options from a personal point of view. Ultimately, decision aids are tools that promote communication, but they do not replace the role of the physician–patient relationship or meaningful conversation during SDM.

A standard grading system for decision aids has been developed. The International Patient Decision Aids Standards (IPDAS) collaboration has developed a system to grade the components and development process of decision aids; the tool grades decision aids in areas of content, development, and effectiveness [24]. A library of decision aids and their IPDAS grade can be accessed at http://decisionaid.ohri.ca/index.html. A systematic review of the use of decision aids in medical practice showed that patients using a decision aid were more knowledgeable about their condition and had a greater understanding of risks involved in care [25]. It is clear that these tools have an effect on clinical care, and there is a need for further study as their use increases.

Family and Community Issues

Clinical decision making is often a complicated process. Physicians may be tempted to predict patient preferences using a framework that is "rational" or "logical." However, patients may value certain emotional, ethical, and community values over a simple rational approach to decision making. *Individuals* interact with the healthcare system, but each individual is also part of a larger community. Each community can be defined by geographic, racial, economic, and educational influences. Within a community, individuals also may strongly associate with a particular subset defined by vocation, avocation, gender, familial status, or sexual preference. Complex social dynamics play a role in the medical decision-making process. Family physicians can be thoughtful about these issues, but may not have insight into the exact definitions or forces involved. Qualitative research is a tool that physicians can

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use to understand the social, emotional, and experiential phenomenon that their patients experience. Understanding and appreciating these forces can help in the implementation of evidence-based care.

Conclusion

The concepts of EBM have evolved over time, and significant work has been done to simplify the process of incorporating the best evidence into care. Our understanding of healthcare delivery will change as EBM becomes more incorporated into daily patient care. Screening tools, diagnostic methods, and treatment options will be refined. Physicians who use the tools within the EBM process can efficiently incorporate meaningful changes into their practice. Family physicians who embrace these tools in their daily practice should be comfortable knowing that they are providing the best possible care for their patients.

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Population Health: Who Are Our Patients?

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Introduction

The US health care is currently undergoing a fundamental transformation. "Population health" is emerging as an important component in a changing system that has traditionally focused on individual patients and encounters.

The Institute of Medicine (IOM) formed the Committee on Quality of Health Care in America in 1996. Two pivotal committee reports identified significant problems with safety and quality in the US health care [1, 2]. Unsafe and fragmented care, under-adoption of health information technology, inadequate application of scientific evidence, and growing complexity of chronic disease in an aging population, were all identified as significant challenges for a delivery model that was "overly devoted to dealing with acute, episodic care. . ." and would "require a fundamental, sweeping redesign of the entire health system" [2]. Two key drivers of this transformation are disappointing performance on measures of health care quality and rapidly escalating health care costs. The USA has consistently demonstrated low rankings in both when compared to many "like" countries with similar economic, social, and political environments [3].

Quality: Evidence consistently shows that the USA lags behind other countries in health measures such as infant mortality, life expectancy, and mortality from causes considered amenable to medical care [4]. Americans only get 54.9 % of evidence-based "recommended care" [5]. More discouraging is a decade of minimal improvement in a majority of the quality measures reported by the National Committee for Quality Assurance (NCQA) for insured patients. Only 52–74 % of women get a mammogram according to evidence-based guidelines, and 45.6 % of diabetics in the Medicaid program have poorly controlled diabetes (A1C $>$ 9 %) [6]. Hospital readmission rates within 30 days of discharge (many avoidable) exceed 20 % for Medicare patients with chronic diseases such as CHF, COPD, and chronic renal failure [7]. The current system does a poor job of identifying patients with gaps in care, ensuring automatic reminders for providers and patients, and providing support and motivation for patients to adopt healthy behaviors and manage chronic illness.

Cost: Health care costs of $2.9 trillion a year account for 17.4 % of the US GDP (up from 7.2 % in 1970) [8]. $9,255 per American is twice the spending of many countries reporting better health outcomes and performance on measures of quality and access [3]. From 2000 to 2010, premiums for health insurance paid by workers have increased at four times the rate of their earnings, with greater increases in recent years, as employers shift more costs to patients. Rising costs are in part related to waste and duplication of services, overtreatment, poor coordination of care, and failure of care delivery in areas of prevention and patient safety. The IOM recently estimated the extent of this waste and ineffective treatment at 30 cents of every health care dollar spent [9]. The dramatic increase in chronic disease accounts for more than 80 % of health care costs. Utilization is highly concentrated, with 5 % of patients accounting for 50 % of health care spending [10].

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Rising costs, waste, gaps in care, and care coordination are poorly addressed by a delivery model that has traditionally focused on one patient, one episode, and one disease, and is encounter-driven and "acute care"-oriented. Patient care is tied to face-to-face encounters with a provider, yet encounters may not occur due to poor access, lack of insurance, or inadequate reminders. If encounters do occur, overburdened primary care providers, who are often solely responsible for the prevention and treatment of acute and chronic illness, do not have the time, the information, or the team support to address all care gaps and patient needs.

Recently, the "Institute for Healthcare Improvement" (IHI) proposed the "Triple Aim," suggesting that improving the US health care system requires the "simultaneous pursuit of three aims: improving the experience of care, improving the health of populations, and reducing the per capita costs of health care" [11]. Evolving models of care such as the "Patient-Centered Medical Home" (PCMH) and "Accountable Care Organization" (ACO) recognize that understanding the patient population served can improve care quality and identify opportunities for cost savings. This emphasis on population health also has the potential to identify high-risk and vulnerable patients and to impact social, behavioral, and economic determinants of health not adequately addressed in our current system.

Defining Population Health

Defining "population health" is not simple and may be viewed differently from a health care delivery versus a public health perspective. The term "population" commonly refers to "the whole number of people or inhabitants in a country or region" where a group is defined in geopolitical terms. Another definition is "a body of people or individuals having a quality or characteristic in common" [12]. Different views and definitions of patient populations have resulted in various approaches to improving population health. Patients with poorly controlled diabetes in a family medicine practice and the women age 50–74 in an Accountable Care Organization who have not had a mammogram are both very useful examples of populations amenable to improvement efforts. Population in this context is best described by the terms "population medicine" and "population management," concepts very useful to a medical system or physician practice in identifying patients who need reminders or outreach for recommended medical interventions. Concern exists that this concept of "population health" may not be broad enough to identify upstream and perhaps more important social, economic, and behavioral determinants of health. Does that poorly controlled diabetic live in a healthy community that fosters good nutrition and exercise? Does the woman needing a mammogram lack insurance or transportation?

The "World Health Organization" (WHO) defines health as "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity" [13]. To achieve health defined in this way will require a broader, more community-based view of the population being served. Kindig has described "the health outcomes of a group of individuals, including the distribution of such outcomes within the group" and has proposed a model with mortality and life quality as outcomes where disparities in achieving good outcomes exist and where determinants affecting these outcomes include not just the quality of health care but also individual behaviors, social and environmental factors, and genetics [14]. This more comprehensive definition of population health has been called "Total Population Health" by Jacobson and Teutsch [15] and considers the health of all people in a geopolitical area. Targeted performance improvement activity by physicians and health systems will be helpful in clinically defined "subpopulations," but improving the health outcomes of the total population in a comprehensive way will require collaboration from multiple stakeholders including public health, government, medical providers, employers, and community leaders. The IOM recently initiated a Roundtable Discussion on Population Health with this goal in mind [16].

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Populations in Primary Care (Who Are Our Patients?)

The IOM call for health care transformation has resulted in new and evolving models of care delivery that are the blueprints for building an advanced system of integrated and patient-centered medical homes and neighborhoods with a focus both on the populations and individual patients. The "American Recovery and Reinvestment Act of 2009" (ARRA) has encouraged electronic health record (EHR) vendors to develop helpful tools, and EHR certification mandates functionality that supports practice-based population management. Incentives provided through the "Meaningful Use" (MU) program have markedly increased EHR adoption by providers. The "Patient Protection and Affordable Care Act" (PPACA) advances population health by expanding insurance coverage for uninsured patients, promoting "Accountable Care Organizations" (ACO) and establishing new value and population-based reimbursement programs such as the Medicare Shared Savings and the Value-Based Modifier programs. The ACA has several provisions that encourage research and innovations around quality and value that will help to achieve the Triple Aim. These blueprints, tools, and financial incentives will help family physicians build advanced medical homes with population health capabilities. Populations and "subpopulations" relevant to family physicians include patients in the medical home, neighborhood, and in the community.

Patients in Our Medical Home (Practice Population)

Registry function: Identifying the patients in a practice (usually defined by encounters) is critical for a successful population management. A patient "registry" allows for queries that search, filter, and group patients and identify important clinical information. Registry function is possible in a paper practice but is limited by manual entry and effort to keep data current. Accurate, complete, and automatically updated patient data is a major benefit of EHR adoption and recent MU standards. The first stage of MU required EHR entry of structured, searchable data including patient demographics like age, race and ethnicity, active problems, medication lists, allergies, vital signs and BMI, smoking status, office encounters, and results such as lab testing and immunization administration. Information such as the number of patients with chronic illness in a practice and age and gender distribution allows for "practice-based learning" and provides physicians valuable insight into the care they need to provide.

A registry enables a practice to group patients by chronic disease and health maintenance needs and to identify gaps in care. The number of diabetics in a practice and those overdue for a yearly eye exam, patients prescribed a recalled medication, or children overdue for vaccinations are all examples of "patient lists" easily generated from a practice registry. Registries can help to stratify risks for a practice population and identify patients who would benefit from additional support. Risk categories are useful for grouping patients with similar needs [17]. Higher risk groups account for disproportionate health care spending and utilization of resources and include patients with multiple or poorly controlled chronic diseases, terminal illness, chronic pain or substance abuse, depression, and cognitive impairment. Frequent office visits or hospitalizations and polypharmacy are additional markers of risk that are searchable with a registry. Physicians can review identified patients and determine the need for *care management*. Other at-risk or vulnerable patients include those with multiple emergency room visits, the uninsured or underinsured, and those with social or economic challenges such as poverty, unemployment, or unsafe living situations. These factors are not easily identified by an electronic health record or practice registry nor easily addressed in the traditional practice model.

Meaningful Use stage 2 certified EHRs do provide some registry functionality, including the ability to generate such *patient lists*. Physicians value the ability to update and customize patient queries and reports, not always possible with some EHR reporting. Additional registry software that can analyze the

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data present in an EHR and generate provider-friendly custom lists and reports can add significantly to population management.

A *health risk assessment* is another valuable practice tool, also used by insurance companies, to risk stratify patients. Dartmouth College has developed *howsyourhealth.org* and *healthconfidence.org*. These no-cost, patient-administered tools can identify patient risk factors and functional limitations and provide patient feedback on quality of care and confidence in self-care. Physicians and patients who develop care plans as a result of the health assessment have shown improvements in care. High health confidence and patient engagement in their own care correlate with better health outcomes, better patient experiences, and less costly care [18]. Practices can positively influence patient health confidence by providing quality health information and good access to care [19].

Patient and provider reminders: Registry and EHR technology can automatically generate provider, care team, and patient reminders based on scientific evidence. This "Clinical Decision Support" (CDS) functionality is an MU requirement. Care team members can address reminder alerts at the point of patient care. Registry searches produce "lists" of patients who have not been seen and need care such as screening and lab testing, immunizations, or office follow-up. Reminders can be sent via mail, personal or TeleVox calls, or preferably secure patient portal messaging.

High functioning care teams: In the traditional encounter-driven "Acute Care Model" (ACM), the physician is responsible for all patient care tasks. A typical primary care panel of patients requires 7.4 h a day to meet preventive care needs and 10.6 h to manage all chronic conditions [20]. It is not surprising that many patients do not receive recommended care or that primary care physicians are at high risk of burnout [21]. An aging population and a relatively smaller primary care workforce will increase the problem. Recent advanced practice models emphasize team care with each member of the care team performing duties at the top of their license. Shared responsibility ensures all patients in a practice population get what they need. Practice teams require clearly defined roles for clinical and nonclinical members. Pre-visit planning and communication via daily *huddles* help foster quality and efficiency. Medical assistants and nurses use rooming protocols that include medication reconciliation, registry reminders to close gaps in care, and ordering protocols for immunizations, screening, and lab testing. *Panel management* by clinical staff includes outreach via phone or patient portal to ensure all care gaps are addressed in the population. Medical assistants can take on the role of health coaches, providing education on lifestyle and chronic disease management. Front desk personnel can help coordinate referrals to ensure proper transitions of care and help with patient outreach, reminder, and follow-up. Medical records personnel can satisfy alerts and reset reminders when test results are received and can track to completion ordered tests and referrals that have not been received.

Advanced primary care practices are utilizing RNs for complex "Patient Care Management" (PCM). These care coordinators support patients with poorly controlled chronic disease, encourage self-management, and coordinate care transitions such as hospital emergency room follow-up. Embedded care managers promote shared decision making and care planning involving patient and physician. Team care has led to outcomes such as lower readmission rates, better control of chronic disease, better medication adherence, and lower costs [22].

Recently, many commercial insurers have provided care management fees to practices with these capabilities. Centers for Medicare and Medicaid Services (CMS) payment reforms reimburse practices for team care with new transition of care, annual wellness visits, and, more recently, "Chronic Care Management" (CCM) codes that pay for care coordination performed by nonphysician care team members. Reports that have examined these high-functioning primary care practices show better patient, physician, and staff satisfaction, increased patient access, and increased revenue to support transformation [22].

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Measurement and reporting: Practice-based learning and continuous improvement is an important competency for a primary care practice. It requires measuring performance around process and outcomes of patient care. EHR and registry technology provide a practice with the tools to develop practice scorecards based on nationally recognized quality measures. CMS provides incentives for measuring quality and aligned metrics in the "Physician Quality Reporting System" (PQRS) and the MU program. Rewards or penalties based on performance are part of the "Value-Based Modifier" (VBM) program. These value initiatives are population based and include measures of practice performance on quality, cost, and patient experience. Sharing how the practice is doing with team members and patients, along with organized efforts to continuously improve performance, is an important standard incorporated into advanced care models such as PCMH.

Patients in Our Neighborhood (ACOs and Integrated Networks)

New care delivery models such as PCMH can improve quality and decrease waste and fragmentation of care [23]. Achieving significant progress toward the Triple Aim, however, will require family physicians to embrace a broader view of population and to coordinate effectively with the specialists and hospital systems that provide care for their patients. Such coordination has been recently described in the position paper, "The Patient-Centered Medical Home Neighbor (PCMH-N): The Interface of the Patient-Centered Medical Home with Specialty/Subspecialty Practices" and standardized by the "Patient-Centered Specialty Practice" (PCSP) NCQA recognition program [24]. The ACA promotes population care at the network level with the concept of ACO's and other value and population-based initiatives. Commercial payers are also experimenting with new reimbursement models around quality and care management as they develop agreements with "Clinically Integrated Networks" (CINs), a term now used interchangeably with ACO in describing a collaboration of primary care providers, specialists, and other providers to improve care. Early evidence indicates that integration at this level can improve quality measures and the patient experience and lower the cost of care [25]. Primary care and the PCMH are at the core of these networks, and the patient populations served are defined by a relationship with a primary care provider. Physician leadership and direction with a goal of improving quality is a Federal Trade Commission requirement of clinical integration and likely critical to achieve the Triple Aim. Primary care providers must take on leadership roles and understand the key principles in managing the health of this larger patient population.

Patients in the neighborhood *(patient attribution*): Medicare attributes patients to an ACO using a two-step attribution process. Most patients are assigned having received a majority of "primary care services" from a primary care physician (step 1). Patients not seeing a primary care provider are attributed based on a majority of ambulatory visits with a specialty provider (step 2). Commercial payers frequently follow similar PCP assignment models based on plurality of visits. Importantly, these methods of PCP/patient attribution may not always align with the perception of the patient or the provider.

Contracts with private CINs often involve populations defined by larger self-insured employer groups, and network collaboration with the employer is important. Quality performance and care coordination of the entire population served by an ACO is the responsibility of all network providers. This global population view is critical for network success but will require a change in thinking for physicians who have been trained and practiced in an encounter-driven, fee-for-service system.

"Network Registry" (Big Data): A network can bring family physicians population management resources not available to smaller independent practices. Data is more complete, as these registries can aggregate data from multiple sources including labs, EHR feeds, hospitals, pharmacies, state immunization registries, insurer claims, and physician member billing claims. Physician encounters and payer

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attribution define the network population. Combining this encounter data with comprehensive clinical information allows for accuracy of quality measures and reporting functionality not available to physician practices. Payer partners provide total costs of care information and the ability to identify cost saving opportunities not available from other sources. Risk analysis and *predictive modeling* tools can group patients by risk groups for effective care management and identify areas of inappropriate utilization. Information on ER use, avoidable hospital admissions and readmissions, medication prescribing and adherence, and unnecessary diagnostic testing is very helpful in planning interventions to improve outcomes and decrease cost of care. For practices unable to support care managers internally, provision by ACOs is highly effective. Commercial payer contracts provide a care management fee to networks for care coordination done in partnership with physicians who have an established relationship with the patient, an important advantage not available in traditional payer disease management programs.

Collaboration: Physician networks provide an infrastructure that facilitates working relationships among the primary care, specialists, hospital system, and other providers. Coordination of improvement efforts based on data and evidence-based guidelines, transparent reporting of performance on quality metrics, identification of opportunities to reduce cost as outlined in the "Choosing Wisely" initiative [26], and commitment to best practice and success for all network providers are key elements for network success. Active physician engagement, leadership in governance, and decisions on quality initiatives, contracts, and incentive distribution differentiate ACOs from the managed care "gatekeeper models" of the 1980s.

Payment reform: Fee-for-service has been the predominant payment model in the US health care and rewards volume and utilization. "Value-Based Payment" (VBP) rewards good outcomes, supports primary care and care management, and reduces unnecessary spending. Current value/population payment models include care management fees, incentive for quality performance, and sharing in network-generated savings. Shared savings programs have been criticized for putting networks and providers at risk, even in "no risk" models, because significant up-front investments are required that may not be recouped. Additionally, year-to-year savings are not likely to be sustainable in the long term. Alternative payment models have been suggested: "fee-for-service" (FFS) for desired care such as immunizations or unavoidable events such as accidental injuries, "episode-of-care payment" and "bundling" for an entire episode of care such as labor and delivery or major joint replacement, and "comprehensive care payment" for care of chronic illnesses like diabetes and CHF, with risk adjustment based on patient population complexity [27]. All have advantages and disadvantages. Networks provide the framework where trusting relationships can develop and communication can occur among all providers and stakeholders so that Value-Based Payment models can be tested and continue to evolve.

Total Population Health

As previously discussed, addressing practice populations with the use of data tools such as patient registries provides the opportunity to examine specific intermediate outcomes based on patient characteristics, provider interventions, or other parameters. This approach, or "population medicine," is characterized by a relationship (physician to multiple unique patients registered in the practice). A wider focus on the health of all those individuals in our geopolitical area (Kindig's "Total Population Health") [14] compels providers to consider a broader range of behavioral, community/environmental, social, and physical factors that influence health outcomes, beyond the quality of clinical practice or even population-based medicine. Family medicine has a rich history of connection with our communities, as the discipline was born out of the 1960s, with its focus on social justice and expanding access to primary care [28]. As many new academic departments of family medicine were founded, they found expression in the "Community-

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Oriented Primary Care" (COPC) model developed in South Africa by Kark and Cassel and interpreted in this country by Nutting [29] and others. This movement included their mission for the underserved and uninsured in their title as departments of family and community medicine. Also developing in the 1960s was the concept of the community health center [30, 31] serving not only those in the center's panel but also the community in which the center was located, often with leadership from the community. The *multidisciplinary teams* assembled by community health centers, including physicians and nurses, educators, social workers, lay health workers, and sometimes dental practitioners, could begin to address the multifactorial "social determinants of health" (SDH) in communities, in addition to providing needed medical care. This model of varying professionals bringing their respective lenses for a sharper focus on patient-centered care within the context of their families and community is the one that has broad application today (the assemblage of professionals now called "interprofessional teams").

Fast forward now to the previously cited fact that the USA spends almost twice as much for per-person health care than any other country yet with very poor outcomes in measures of the health of the population. Could this be a widespread poor quality of health care that is being provided, or are there other explanations for this *health gap* between the USA and other developed countries? Certainly, waste within the system accounting for one-third of total health care expenditures is a huge reason for relatively costly care in the USA, with the startling irony that this waste diverts dollars in the federal budget away from other areas that play a substantial role in health outcomes, such as education and employment opportunities [32].

Camara Jones describes the range of factors affecting "health outcomes" using concentric circles [33] with "health behaviors" at the center of determinants (explaining ~80 % of outcomes) and "social determinants of health" as the next level (e.g., education and health literacy; socioeconomic status affecting opportunities and resources). But Jones describes yet another concentric circle in this diagram: "social determinants of equity." For example, "zip code matters" in determining rates of infant mortality or differential spending per student among school districts affecting whether or not a child has access to early childhood programs: an intervention highly correlated with health outcomes later in life. Jones' metaphor of "red flowers and pink flowers" also illustrates how institutionalized, interpersonal, and internalized racism lead skin color to be mistaken for "hardwired" risk for disease (and therefore beyond our control, opportunity, or responsibility for addressing disparities in health outcomes).

Medical training has been filled with examples of ways that we learn to "blame the patient" for poor *outcomes*, including the label of "noncompliance" with treatment plan when cost of pharmaceuticals, even generics, makes their purchase beyond reach for some, provider attitudes toward obese patients regardless of underlying predisposing national policies and environmental influences [34], and office policies that a patient will be dismissed for the third "no show." However, when motivated by PCMH principles to drill down on suboptimal outcomes such as the "Did Not Keep Appointment" (DNKA) list, many practices find that transportation (e.g., "my Medicaid ride didn't come") leads the reasons for "DNKA," and practices that track *High Emergency Department Utilizers* find thoughtful reasons for going to the ED instead of the primary care office (e.g., not risking losing a day of work without being seen or having all tests/consultations done at once) [35].

All these and other barriers to access to care illustrate the "social determinants of health" (e.g., higher poverty, obesity, and stress levels) that partly explain the USA's relatively poor *health rankings*. They must be addressed to improve overall health in the population. Within the medical home, building *interprofessional teams (*nurses as care managers, pharmacists, social workers, community health workers, legal aid) to help address these barriers have been reported to be highly effective in reducing readmissions and unnecessary emergency department use [36]. The Camden Coalition of Healthcare Providers identified "super-utilizers" of emergency department services through a city-wide database of ED use and organized a system that improves coordination and quality of care and at the same time reduces cost [37].

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This perspective represents a major shift from the more limited approach of seeing patients who come to us and attempting to provide the best possible care, often dismissing those who do not keep their appointments with us or labeling those unable to follow the treatment plans we prescribe as "noncompliant." In a population-based system in which the goal is to facilitate improved *health status* among individuals in the community served, providers must measure the effect of interventions or services in populations receiving them; seek to improve outcomes of care, i.e., quality improvement; search for those factors (social determinants of health) that prevent our population from reaching a state of *optimal health and function*; and identify and work toward potential solutions for those factors that lead to unequal and unjust health outcomes within our community (*social determinants of equity or disparities*).

Who Is Accountable for Individuals in Our Community?

So how can family physicians act within their practices, or practice group, or delivery system, or as motivated citizens to bridge the gap between focus on health outcomes for their patient panel and improving health at the level of their community? One familiar intervention that spans care of individuals and community health is preventing by counseling and screening for and treating sexually transmitted illness (STI) that in turn reduces the spread of the STI within the community. Active engagement in identifying and modifying when possible the common risk behaviors that together account for a substantial proportion of mortality (tobacco use, poor nutrition, physical inactivity, and unhealthy alcohol use) is imperative to offer to patients within one's practice. This focus on prevention can also extend to the community by offering options such as smoking cessation workshops, advocating for removal of unhealthy food choices in school vending machines, and supporting community resources offering alcohol and substance abuse prevention and treatment. Sponsoring "Walk with my Doc" Saturdays, promoting national initiatives such as the "Million Hearts Campaign," and serving on one's local or state Academy's Health of the Public committee can have ripple effects in the community and beyond. At another level, the difference between clinical practice with focus on individual behaviors *relative risk* versus *attributable risk* in populations (as defined, e.g., by census tract, average income level, or prevalence of crime) highlights a strength of the population-based approach. Physicians can examine the distributions of health outcomes within their practices and potentially identify the factors behind disparities thus identified. Electronic health records now commonly can produce reports of distributions of physiologic outcomes (e.g., blood pressure or A1C) by a provider or practice and in some cases by the age of the patient, or self-identified race, or comorbid disease state. The next level identifying not only the community or census track where the patient/family lives but also identifying the *community vital signs* known to convey attributable risk (or protection) to those who reside in that area could be of considerable importance in recognizing factors associated with poor treatment response or *disparities in outcomes*.

Collaborating with the multi-sectoral health system in *coalitions* of organizations whose core mission is addressing *upstream factors* for health may be beyond the motivation or ability of an individual physician. But physician organizations can through representatives participate in such *coalition*, not necessarily as leaders but by bringing their perspective as health care providers to clinical/community partnerships, with members of the community defining the issues most important to the health of the community. Physicians' influence with *change agents* from the community, including those in business, government, and other policy-makers can be instrumental in shifting toward alignment of incentives for improved health across the spectrum of stakeholders. Family physicians can build on a foundation of primary care-based patient-centered medical homes, integrating with the patient-centered neighborhood of specialty care all embedded within accountable care communities. These structures will increase possibilities and incentives for addressing upstream determinants of health and equity and give us the opportunity to achieve the higher level of total population health that we seek.

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Clinical Prevention

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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 issues of high-priority objectives, four of which apply directly to clinical prevention. Improvement has been recorded in three of these areas: colorectal cancer screening, increasing from 52 % in 2008 to 59 % in 2010, with a target of 71 % by 2020; the percentage of adults with hypertension whose blood pressure is under control, increasing from 44 % in 2005–2008 to 49 % in 2009–2012, with a target of 61 % by 2020; and childhood immunization, with the percentage of children receiving recommended doses of DTaP, polio, MMR, Hib, hepatitis, varicella, and PCV vaccines by ages 19–35 months increasing from 44 % in 2009 to 69 % in 2011 with a target of 80 % by 2020. In contrast, there was little or no detectable change for diabetes control, which only increased from 18 % in 2005–2008 to 21 % in 2008–2012 [1]. Additional data has shown that only 28 % of smokers received recommended preventive care, 37 % of adults aged 50 and older received a flu vaccination, and only 40 % of sexually active young women received annual screening for chlamydial infection [2].

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

Three key recommendations from the USPSTF – tobacco cessation screening and assistance, discussing daily aspirin use, and alcohol counseling with brief counseling – were cited as examples of services that could contribute significantly to net additional yearly medical savings if delivery were increased [3]. Along with colorectal cancer screening, an increase to 90 % delivery would have contributed 100,000 years of life to the US population in 2006. Recommendations concerning aspirin [4] were tempered in May 2014 when the Federal Drug Administration (FDA) cautioned that the totality of evidence for primary prevention is not yet sufficient to make general guidelines for aspirin prescription [5]. The FDA advised that individual clinical judgment by providers is required [5]. Additionally, it was noted [3] that childhood immunizations as recommended by ACIP could save 1,233.1 life years per 10,000 people per year of intervention at an annual net savings of $267 per person per year in medical costs.

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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 rescreening 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 to 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, 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 the number of false positives increases, thereby increasing sensitivity and decreasing

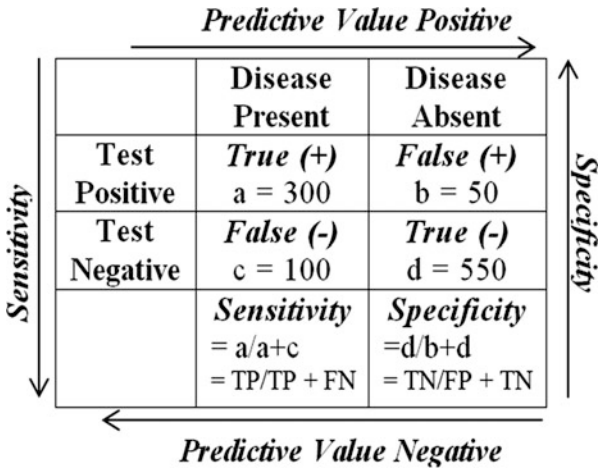

Fig. 1 Sensitivity and specificity of screening tests (As the cutoff criterion decreases, the number of false (−) decreases, while the number of false (+) increases, thereby increasing sensitivity and decreasing specificity. In contrast, as the cutoff criterion increases, the number of false positives decreases, and the number of false negatives increases, thereby increasing specificity and decreasing sensitivity)

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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 the 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) = 350/1,000 = 35 % = proportion of persons being tested who have the disease.
- Accuracy = (a+d)/(a+b+c+d) = 850/1,000 = 85 %. If the prevalence of the disease being tested differs in two populations 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. Also the evidence base for clinical prevention is rapidly evolving. Therefore, while we have endeavored to provide current information in this chapter, providers should keep track of evidence and recommendations as they appear and treat patients accordingly.

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 US 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

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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. All such services are mandated for coverage as part of the Affordable Care Act (ACA). As Task Force recommendations are regularly updated, the ePSS (Electronic Preventive Services Selector) is a convenient tool to identify recommended services based on the patient's sex, age, pregnancy status, tobacco use, and sexual activity. It is available at http://epss.ahrq.gov/PDA/widget.jsp. 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 annual reviews and updates of the recommended immunization schedule. 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. 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., postexposure, travel and occupational prophylaxis, screening for tuberculosis, etc.) may be found in other chapters in this volume.

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

Immunization

***Birth to eighteen 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 14 vaccine-preventable diseases before age two. 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 more than 90 % of children aged 19–35 months are getting the recommended vaccines, booster shots and second doses lag for 2-year-olds [8]. 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 Immunizations website provides the catch-up schedule. An Instant Childhood Immunization Scheduler is also available at http://www2a.cdc.gov/nip/kidstuff/newscheduler_le/. 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 [9]. Annual influenza vaccinations for all persons aged ≥6 months and "catch-up" vaccinations such as measles, mumps, and rubella (MMR), hepatitis B, and varicella vaccinations are also recommended [9]. See Fig. 2.

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*:** *Ocular Prophylaxis for Gonococcal Ophthalmia Neonatorum* should be provided within 24 h of birth. At present, 0.5 % erythromycin ophthalmic ointment is the only approved drug approved for this purpose by the US Food and Drug Administration.

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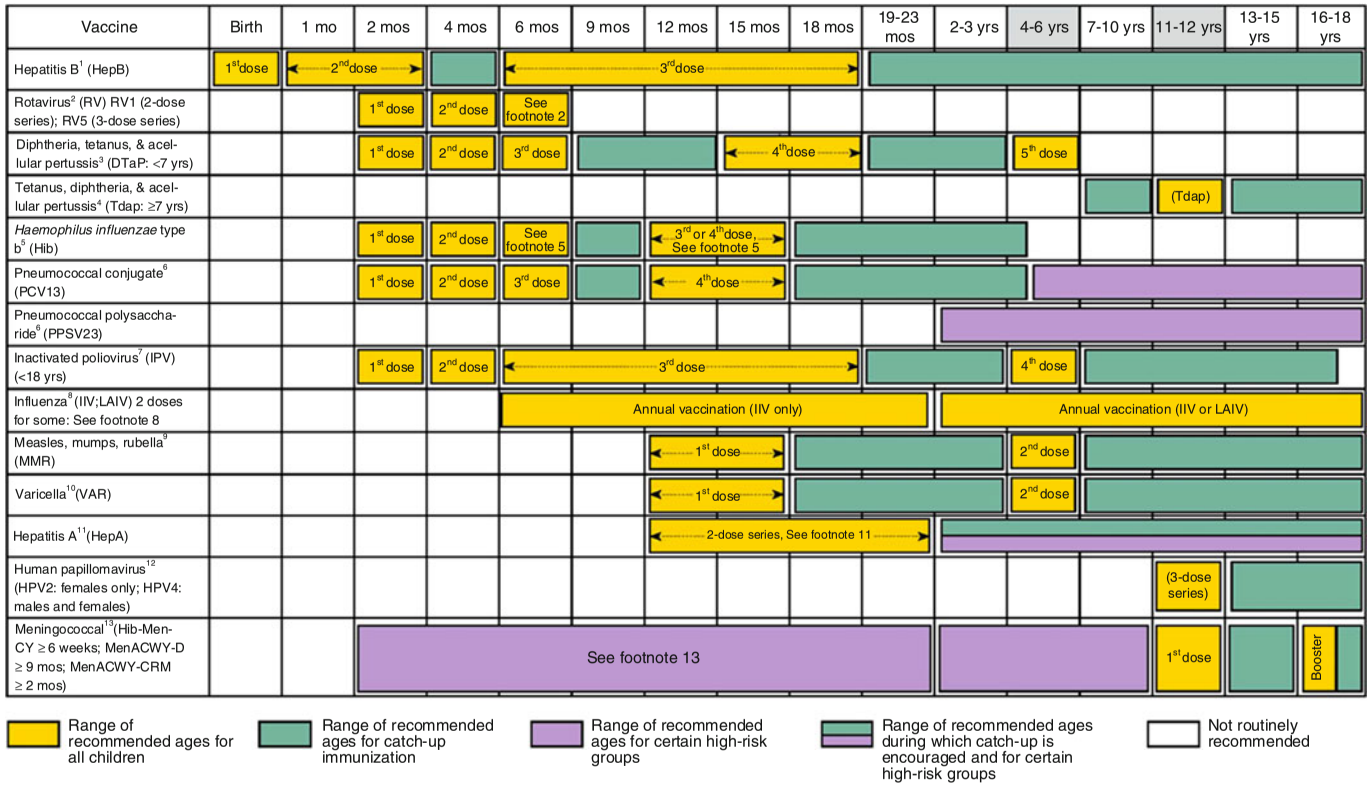

Fig. 2 Recommended immunization schedule for persons aged 0–18 years – United States, 2014 (Note: The above recommendations must be read along with the footnotes of this schedule. See: http://www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf. This schedule includes recommendations in effect as of January 1, 2014. Any dose not administered at the recommended age should be administered at a subsequent visit, when indicated and feasible. The use of a combination vaccine generally is preferred over separate injections of its equivalent component vaccines. 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).). Suspected cases of vaccine-preventable diseases should be reported to the state or local health department. Additional information, including precautions and contraindications for vaccination, is available from CDC online (http://www.cdc.gov/vaccines/recs/vac-admin/contraindications.htm)

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***Six 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 of fluoride]). The USPSTF recommends routine supplements with iron for asymptomatic infants aged 6–12 months who are at increased risk for IDA. *Folic acid* prophylaxis (400 micrograms per day) is recommended for females beginning at age 15 years in order to prevent spina bifida and anencephaly, in part because more than half of pregnancies are unplanned and because these birth defects occur during the first three to four weeks of conception, when many women are unaware they are pregnant.

Counseling and Anticipatory Guidance

***Birth to two years*:** Counseling and anticipatory guidance during the first 2 years of life may decrease hospitalizations among children irrespective of race and health status, especially among the socioeconomically vulnerable [10]. 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 ear infections, respiratory tract infections, and incidence of gastrointestinal infections. Furthermore, studies also show that breastfed children are less likely to present with asthma, type 2 diabetes, and obesity [11]. 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 HIV infection 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 shows 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 include recommendations for a safe sleep environment for all infants such as firm sleep surface, breastfeeding, room-sharing without bed-sharing, and avoidance of overheating and exposure to tobacco smoke, alcohol, and illicit drugs [12]. Children are particularly vulnerable to the effects of *secondhand smoke*. It increases the risk for SIDS, asthma, otitis media, and lower respiratory tract infections [13]. The American Academy of Family Physicians (AAFP) strongly recommends that physicians counsel smoking parents with children in the house regarding the harmful effects of smoking and children's health.

Primary prevention with provider counseling to include environmental assessments is recommended by the CDC prior to screening for elevated *blood lead* levels in asymptomatic children who are at increased risk. Children who are on Medicaid, living in poverty, and living in older housing are considered to be at especially high risk (USPSTF Grade: I). 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. Until recently, the CDC used a *blood lead* level result of 10 or more micrograms per deciliter (μg/dL) as a "level of concern" with respect to screening for lead exposures. In 2012, the term "reference value" $\geq$ 5 μg/dL was introduced to identify children who have been exposed to lead and who require case management. Confirmatory testing, ongoing monitoring of blood lead level, and assessment of iron deficiency and general nutrition (e.g., calcium and vitamin C levels) are also required. The recommendation for medical treatment (tertiary prevention) is chelation for lead levels $\geq$ 45 μg/dL.

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The American Academy of Pediatrics issues extensive policy statements on the prevention of *drowning*, including the use of direct counseling, handouts, websites, and other educational materials as well as specific targeted messages to children with special risks. Community efforts should also be supported [14].

***Three to ten 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 television and other screen time to no more than 2 h/day [15]. The US Department of Health and Human Services (DHHS) recommends that children participate in at least 60 min of physical activity daily. Parents should be encouraged to motivate their children to 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 [14]. Most deaths of children aged 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 are among the most important preventive measures to reduce motor vehicle-related injuries and deaths [16]. The AAP recommends that infants and toddlers should ride in a rear-facing car seat until they are at least 2 years old.

***Eleven to eighteen 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 aged 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, to wear protective clothing, and to use sunscreen as directed [4].

An evidence-based statement from the American Dietetic Association recommends using *family-based lifestyle interventions* for children and adolescents. 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 [4]. Cyberbullying is associated with *mental health and substance use* problems in adolescents. 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 available through recognized organizations such as Bright Futures (http://www.brightfutures.org/mentalhealth/pdf/families/mc/bullying.pdf).

All sexually active adolescents are at risk of *sexually transmitted infections*. In 2013, 34 % of 9th through 12th grade American students reported having sexual intercourse within the last 3 months, and only 59 % used a condom during the last episode [14]. Family physicians should provide high-intensity behavioral counseling to prevent STIs including HIV infection and unintended pregnancy. *Tobacco* use is the main cause of preventable illness and death in the United States, accounting for more than 480,000 deaths per year or 1,300 per day [17]. Most smoking and smokeless tobacco use begins in youth and young adulthood. In 2012, 23.3 % of high school students and 6.7 % of middle school students reported current use of any tobacco product [18]. Education and counseling reduces the chances children and teens

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will start smoking. Interventions include direct counseling with teens individually 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 the USPSTF and the American Academy of Pediatrics (AAP) screening recommendations are summarized in Tables 1 and 2.

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

Recommendation	USPSTF[a]	American Academy of Pediatrics[b]
Height and weight BMI	Screen children aged 6 years and older; offer or refer for intensive counseling and behavioral interventions	BMI calculated and plotted at least annually
Hypertension	Insufficient evidence to make a recommendation (before 18 years)	Annually beginning at 3 years of age
Newborn blood screening	Congenital hypothyroidism, phenylketonuria, and sickle cell disease	Universal newborn screening (31 conditions)
Critical congenital heart disease	No recommendation	Newborns using pulse oximetry
Hearing loss	Newborn screening but no recommendation beyond the newborn period	Newborn screening. Confirm positive newborn screen by 3 months with comprehensive evaluation. Continue regular assessments throughout childhood
Vision screen	Screen children aged 3–5 years at least once	Assess at 3, 4, 5, 6, 8, and 10 years, and once during each period of early, middle, and late adolescence
Eye prophylaxis	Newborns	Newborns
Iron deficiency anemia	Insufficient evidence to make a recommendation	Hemoglobin at 1 year of age. Risk assessment at 4-, 15-, 18-, 24-, and 30-month visits and annually thereafter
Dyslipidemia	Insufficient evidence to make a recommendation (up to age 20 years)	Assess risk at 2, 4, 6, and 8 years of age. Universal screen between 9 and 11 years of age
Dental caries Prevention, birth to age 5 years	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
Immunization	Refer to Advisory Committee on Immunization Practices (ACIP) http://www.cdc.gov/vaccines/recs/schedules/default.htm	
Speech and language delay in preschool children	Insufficient evidence to make a recommendation (children $\leq$ 5 years of age)	Periodic screening for developmental delays. Administer screening tests at the 9, 18, and 30 month visits
Autism spectrum disorder (ASD)	Topic review in progress	If no concerns have been raised during the course of the preventive visit and the child is not the sibling of a child who has already been diagnosed with an ASD, screening with an autism-specific tool is indicated at 18 or 24–30 months

(*continued*)

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Table 1 (continued)

Recommendation	USPSTF[a]	American Academy of Pediatrics[b]
Major depressive disorder (MDD)	Adolescents (aged 12–18) when systems are in place to ensure accurate diagnosis, psychotherapy, and follow-up. Use Patient Health Questionnaire for Adolescents [PHQ-A] and the Beck Depression Inventory-Primary Care Version [BDI-PC]	
Tobacco use in children and adolescents	Provide interventions to prevent initiation of tobacco use in school-aged children and adolescents: face-to-face or phone interaction with a healthcare provider, print materials, and computer applications	Counseling starting at 5 years against initiating tobacco use and provide counseling on tobacco cessation. Also advise all families to make their homes and cars smoke-free
Alcohol misuse, 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 use 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	Insufficient evidence to make a recommendation	

[a]USPSTF A and B Recommendations. US Preventive Services Task Force. December 2014. With permission from the Agency for Healthcare Research and Quality
http://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. Complete AAP recommendations may be found at http://www.aap.org/en-us/professional-resources/practice-support/periodicity/periodicity%20schedule_FINAL.pdf

***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 31 congenital disorders*, including severe combined immunodeficiencies (SCID) [19]. The USPSTF recommends that infants who are tested for *PKU* within the first 24 h after birth should receive a repeat screening test by two weeks of age [4]. 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

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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

Hyperbilirubinemia: infants of at least 35 weeks' gestation	Insufficient evidence to make a recommendation	Risk evaluation by using predischarge levels individually or in combination with clinical risk-factor assessment
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
Iron supplementation	Routine iron supplementation for asymptomatic children aged 6–12 months who are at increased risk: premature and low birth weight infants; adult females; recent immigrants and, among adolescent females, fad dieters; and those who are obese	Breastfed infants should be supplemented with 1 mg/kg per day of oral iron beginning at 4 months of age until they can be fed with appropriate iron-containing complementary foods
Lead poisoning	Insufficient evidence to make a recommendation in children 1–5 years of age	Blood lead level at 12 and 24 months for patients with Medicaid or in high-prevalence areas
Sexually transmitted infections (STI), counseling	High-intensity behavioral counseling for all sexually active adolescents: provided basic information about STIs and transmission, assess the individual's risk for transmission, and provide training in pertinent skills such as condom use, communication about safe sex, problem solving, and goal setting	Annually beginning at 11 years of age. Counseling for adolescents regarding abstinence and the importance of barrier contraceptives is recommended
Chlamydia/gonorrhea screening	Sexually active women aged $\leq$ 24 years	Sexually active women aged $\leq$25 years at least annually
Hepatitis B virus infection, screening adolescents	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; men who have sex with men; household contacts and sexual partners of HBsAg-positive persons; patients receiving hemodialysis; and immunosuppressed and HIV-positive persons	
HIV infection, screening	All adolescents and adults aged 15–65 years and others who are at increased risk for HIV infection and all pregnant women Note: The AAFP endorses the CDC recommendation to initiate routine screening at age 13 years	Once between the ages of 16 and 18, making 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
Tuberculosis	Refer to the CDC website at http://www.cdcnpin.org/scripts/tb/cdc.asp	Annual tuberculin skin test in children infected with HIV, incarcerated adolescents, those with a family member or contact with TB disease, and those born in or who had recent travel to a high-risk country
Dental caries prevention, birth to age 5 years	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
Skin cancer, counseling	Aged 10–24 years who have fair skin High risk: fair skin, freckles, atypical nevi, >50 mol, increased lifetime or intense sun exposure	Sun safety advice during health maintenance visits at least once per year

(*continued*)

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Table 2 (continued)

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.

recommends 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 two 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* [20]. 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.

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

***Two to ten years*:** *Well-child visits* should occur at 24 and 30 months and once every year thereafter. The family physician should ask questions about 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 in addition to a medical home should be established, and a preventive visit to the dentist should occur twice per year [18]. 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.

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The CDC has recommended growth charts for *monitoring growth* from ages 2 years and older (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 between the 85th and 95th percentiles and ≥95th percentile, respectively. In the last three decades, obesity rates have more than doubled in US children, and recent statistics show that 8.4 % of 2–5-year-olds had obesity compared with 17.7 % of 6–11-year-olds [21]. 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 has given a Grade: I recommendation (insufficient evidence) to 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 aged 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 conditions such as diabetes, obesity, or hypertension [22].

***Eleven to eighteen 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. Obesity has become a major cause of adolescent morbidity, is a contributor to a dramatic increase in the number of youth with type 2 diabetes mellitus, and 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 [4].

Sexually active teens should be screened for *STIs including chlamydia and gonorrhea*. The risk for chlamydial infection is higher among sexually active women 24 years of age or younger. 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). The CDC recommends opt-out HIV testing (i.e., testing is done after notifying the patient that the test is normally performed but that the patient may elect to decline or defer testing) for all patients seen in healthcare settings beginning at age 13 years [23]. 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.

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. Some instruments developed for primary care (Patient Health Questionnaire for Adolescents [PHQ-A] and the Beck Depression Inventory-Primary Care Version [BDI-PC]) have been used successfully in adolescents to screen for MDD.

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The AAP, however, recommends screening annually beginning at 11 years of age using the CRAFFT six-item tool (Car, Relax, Alone, Forget, Friends, Trouble) to screen adolescents for high-risk alcohol use and other drug use disorders simultaneously (Table 1).

Prevention at Ages Over 18 Years

Immunization

Adult vaccination coverage remains low for most recommended vaccines. The 2010 National Health Interview Survey reported that only 18.5 % of adults aged 18–64 years at risk of pneumococcal disease have received the vaccine. Furthermore only 40 % of those at risk for influenza were immunized against influenza during the 2012–2013 influenza season. Limited awareness among the public about vaccine schedules for adults and missing opportunities to incorporate age-appropriate immunizations into routine visits are some of the factors. A recommendation by a patient's healthcare provider for needed vaccines is a strong predictor of patients receiving recommended vaccines [24]. The Community Guide describes additional interventions that could help to increase vaccination rates like routine screening and offering of vaccines and implementation of reminder systems (http://www.thecommunityguide.org/vaccines/index.html). The ACIP annually reviews and updates the "Recommended Immunization Schedule for Adults Aged 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 60 years. For *pneumococcus bacteria*, all adults 65 years of age or older receive a dose of PCV13 followed by a dose of PPSV23 6–12 months later. If a dose of PPSV23 cannot be given during this time window, it should be administered later, 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 illnesses like 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 of age. For patients with diabetes ≥ 60 years of age, 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. All adults without evidence of immunity to *varicella* should be vaccinated against it. 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 spina bifida and anencephaly. 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 [4]. 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

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Recommended adult immunization schedule, by vaccine and age group

VACCINE ▼ AGE GROUP ▶	19-21 years	22-26 years	27-49 years	50-59 years	60-64 years	≥ 65 years
Influenza [2,*]	1 dose annually					
Tetanus, diphtheria, pertussis (Td/Tdap)[3,*]	Substitute 1-time dose of Tdap for Td booster; then boost with Td every 10 yrs					
Varicella[4,*]	2 doses					
Human papillomavirus (HPV) Female[5,*]	3 doses					
Human papillomavirus (HPV) Male[5,*]	3 doses					
Zoster[6]	1 dose					
Measles, mumps, rubella (MMR)[7,*]	1 or 2 doses					
Pneumococcal 13-valent conjugate (PCV13)[8,*]	1 dose					
Pneumococcal polysaccharide (PPSV23)[9,10]	1 or 2 doses					1 dose
Meningococcal[11,*]	1 or more doses					
Hepatitis A[12,*]	2 doses					
Hepatitis B[13,*]	3 doses					
Haemophilus influenzae type b (Hib)[14,*]	1 or 3 doses					

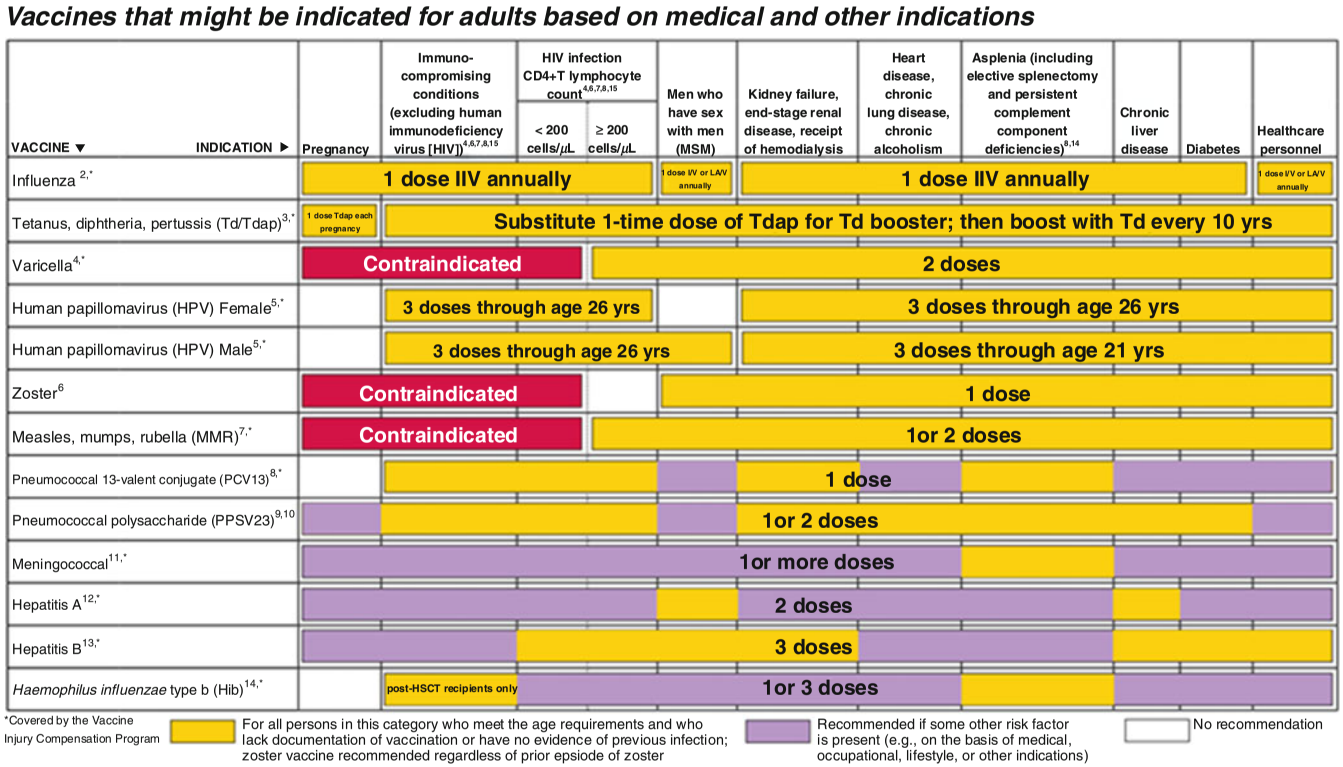

Fig. 3 Recommended Adult Immunization Schedule – United States, 2014 (Note: The above recommendations must be read along with the footnotes of this schedule. See: http://www.cdc.gov/vaccines/schedules/downloads/adult/adult-schedule.pdf. The recommendations in this schedule in effect as of January 1, 2014, were approved by the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP), the American Academy of Family Physicians (AAFP), the American College of Physicians (ACP), the American College of Obstetricians and Gynecologists (ACOG), and the American College of Nurse-Midwives (ACNM). Additional information about the vaccines in this schedule, extent of available data, and contraindications for vaccination is also available at www.cdc.gov/vaccines)

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risk. For women who are at increased risk for breast cancer and at low risk for adverse medication effects, clinicians should offer to prescribe risk-reducing medications, such as *tamoxifen or raloxifene*. Increasing bone strength includes *calcium and vitamin D supplementation*.

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 [25]. 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). Up to 40 % of deaths from leading causes could be prevented by making healthy lifestyle choices.

Counseling comprises recommendations for healthy lifestyle and intensive behavioral counseling for adults known risk factors for *coronary heart disease* and *diet-related chronic disease* and also advise on the importance of regular physical activity including aerobic, strength, and flexibility training in the prevention of disease and nontraumatic 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., CAGE, 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 for reasons that are still not clear. 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 about the adverse effects of obesity, alcohol, illicit drugs, tobacco, and other environmental exposures. If a patient has a BMI >30, recommend weight loss before becoming pregnant. Advise women that there is no known safe level of alcohol consumption during pregnancy and stress the harmful effects of alcohol and illicit drug use on fetal development. Counsel that smoking during pregnancy can cause infant death and is associated with increased risk for premature birth and intrauterine growth retardation. Provide smoking cessation counseling sessions, augmented with messages and self-help materials tailored for pregnant smokers if appropriate.

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

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complete cervical removal) for benign disease, screening is not necessary [4]. For *breast cancer*, family history and age are key risk factors. The USPSTF recommends biennial mammography for women aged 50–74 years, while the American Cancer Society (ACS) recommends that annual mammography begin at age 40 and continue so long as the woman is in good health. Women with a family history suggestive 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 aged 40+ years. Teaching breast self-examination is not recommended by the USPSTF, based in part on data showing that it takes time, increases the rate of breast biopsy for benign disease, and does not result in lower breast cancer mortality [26].

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 reduces mortality. Screening is recommended for all adults aged 50–75 years. Despite compelling evidence of cost-effectiveness, screening rates remain far below what would be necessary to decrease incidence and mortality. Behavioral Risk Factor Surveillance Survey (BRFSS) data from 2012 showed that only 65.1 % of adults in that age group met CRC screening guidelines, and 27.7 % had never been screened. 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, fecal occult blood test (FOBT) cards). *Lung cancer* is the leading cause of cancer-related death and the second most common in the USA. 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. Screening for *prostate cancer* is not recommended. The Task Force guideline applies to 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 prostate-specific antigen (PSA)-based prostate cancer screening are, at best, small and potentially none, and the harms are moderate to substantial potentially due to harms 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. *Hypertension* affects approximately 25–30 % 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 aged 18 and over is recommended by the USPSTF. In addition, the Task Force recommends screening for *type 2 diabetes mellitus* in asymptomatic adults with treated or untreated sustained BP >135/80 mmHg. The USPSTF strongly recommends screening for *lipid disorders* among men 35 years of age and older and for men aged 25–35 years if they are at increased risk for heart

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disease. Comparable recommendations are made for women aged 45 years and older and 25–45 years. The optimal interval for screening is uncertain, although every 2 years for hypertension and every 5 years for dyslipidemia are generally considered reasonable.

Chlamydia and gonorrhea are the most commonly reported STIs in the USA with chlamydial infections being ten times more prevalent than gonococcal infections (4.7 % vs. 0.4 %) in women aged 18–26 years [27]. The USPSTF recommends screening in sexually active women aged 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" refers to clinical staff (e.g., nurse specialists) that 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 [28]. *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 [29]. 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. Interventions for women of childbearing age include counseling, home visits, information cards, referrals to community services, and mentoring support. 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 aged 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 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 adults as the general population, with the rate highest for white men over 85 years of age.

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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. In a large systematic review, the common reasons for provider gaps in preventive care were classified as lack of awareness of guidelines, lack of familiarity with guidelines, lack of agreement, lack of

Table 3 USPSTF A and B recommendations for adults

Recommendations	USPSTF[a]	Other recommendations[b]
Cancer		
Breast cancer, mammography	Biennial screening for women 50–74 years of age. Before age 50 should be individualized and take into account patient's risks and values regarding specific benefits (Grade: C)	ACA: every 1–2 years for women >40 ACS, AMA: annually beginning at 40 ACOG: annually for women ≥40
Breast self-examination (BSE)	Recommends against teaching BSE	ACOG: "breast self-awareness" for women ≥ 20 and can include BSE
Breast cancer, clinical examination	Insufficient evidence	ACOG: annually for women ≥ 40 and every 1–3 years for women aged 20–39
Breast cancer, digital mammography or MRI	Insufficient evidence	ACS, NCCN: annually in addition to mammography for women with a strong family history or genetic predisposition
Breast cancer, prevention medication	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[c]	ASCO: tamoxifen for ER-positive breast cancer in women ≥35 years who are at increased risk. Raloxifene and exemestane for postmenopausal women
Breast and ovarian cancer/ BRCA risk assessment and genetic counseling/testing	Screen women who have family members with breast, ovarian, tubal, or peritoneal cancer that may be associated with an increased risk for BRCA1 or BRCA2. If screening is positive, provide genetic counseling and BRCA testing	ACOG recommends genetic risk assessment for women who have more than a 20–25 % risk for an inherited predisposition to breast and ovarian cancer
Cervical cancer	Women aged 21–65 years with cytology every 3 years or for women aged 30–65 years with cytology plus HPV testing every 5 years	ACS, ACOG same
Colorectal cancer (CRC)	Screening beginning at age 50–75 years: (1) annual high-sensitivity FOBT, (2) sigmoidoscopy every 5 years combined with high-sensitivity FOBT every 3 years, or (3) screening colonoscopy at intervals of 10 years	US Multi-Society Task Force on CRC: beginning at 50 years: (1) annual high-sensitivity FOBT; every 5 years (2) flexible sigmoidoscopy or (3) double-contrast barium enema or (4) virtual colonoscopy; (5) colonoscopy every 10 years; or (6) fecal DNA
Colorectal cancer, genomic testing	No recommendation	The AAFP recommends offering genetic testing for Lynch syndrome to patients newly diagnosed with CRC and to first-degree

(*continued*)

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Table 3 (continued)

Recommendations	USPSTF[a]	Other recommendations[b]
		relatives of those found to have Lynch syndrome (2012)
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	AAFP: insufficient evidence ACS, National Comprehensive Cancer Network (NCCN): adults aged 55–74 years
Prostate cancer	Do not use prostate-specific antigen (PSA)-based screening for prostate cancer	The American Urological Association (AUA) recommends against screening men < 40, average-risk men 40–54, men >70, or men with a life expectancy of less than 10–15 years
Counseling to prevent skin cancer	Children and young adults aged 10–24 years who have fair skin. Limit sun exposure (10 a.m. and 4 p.m.); wear protective clothing and sunscreen (SPF 15 or greater)	
Cardiovascular disorders		
Abdominal aortic aneurysm (AAA), men	One-time screening by ultrasonography in men aged 65–75 years who have ever smoked (≥100 cigarettes) Selectively offer screening for AAA in men aged 65–75 years who have never smoked	The AHA: one-time screening in men aged 65–75 years who have ever smoked and in men ≥ 60 years who are the sibling or offspring of a person with AAA. Does not recommend screening for AAA in men who have never smoked
Aspirin for primary prevention of cardiovascular disease	For men aged 45–79 years when myocardial infarction prevention and for women aged 55–79 years when reduction in ischemic stroke outweighs potential harm of GI hemorrhage	ADA/AHA: aspirin therapy (75–162 mg/d) for persons with diabetes >40 years or who have additional risk factors for CVD and no contraindications
Blood pressure (BP) hypertension	Screening for high blood pressure in adults aged 18 and over	The JNC7[d] recommends every 2 years for adults with BP <120/80 and every year for BP 120–139/80–89 mmHg
Diabetes mellitus type 2: screening	Asymptomatic adults with sustained BP >135/80 mmHg (either treated or untreated)	The ADA recommends a 3-year interval. The AAFP recommends screening in adults with HTN and hyperlipidemia.
Lipid disorders: screening	Men aged 35 and older Men aged 20–35 and women aged 20 and older if they are at increased risk for CHD	ATP III recommends a fasting lipid panel (total cholesterol, LDL, HDL, and TG) in all adults >20 y/o every 5 years
Healthy diet and physical activity: counseling adults with high risk of CVD	Recommends offering or referring adults who are overweight or obese and have additional CVD risk factors to intensive behavioral counseling interventions to promote a healthful diet and physical activity for CVD prevention	The AHA recommends counseling interventions to promote a healthful diet and physical activity (≥2 strategies): setting specific, proximal goals; providing feedback on progress; strategies for self-monitoring; planning for frequency and duration of follow-up; motivational interviews; and building self-efficacy
Obesity in adults: screening and management	Screen all adults for obesity Clinicians should offer or refer patients with a BMI of ≥ 30 kg/m^2 to intensive, multicomponent behavioral interventions	The NIH suggests considering the use of weight-loss medications as part of a multicomponent program if BMI >27 kg/m^2 and if with comorbid medical conditions
Infectious diseases		
Chlamydia and gonorrhea: screening	Sexually active women aged ≤ 25 years and in older women who are at increased risk for infection (prior STIs, HIV, new or multiple sex	The CDC recommends annual screening in all sexually active women ≤ 25 years and in older

(*continued*)

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Table 3 (continued)

Recommendations	USPSTF[a]	Other recommendations[b]
	partners, exchanging sex for money or drugs) Insufficient evidence for screening in men	women who are at increased risk and in MSM, based on exposure history
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	
Hepatitis C: screening	Persons at high risk for infection (past or current injection drug use, blood transfusion before 1992) and one-time screening for adults born between 1945 and 1965	
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)	The AAFP's recommendation differs from the USPSTF only on the age to initiate routine screening for HIV beginning at age 13 years as recommended by CDC
Immunizations	Refer to the National Immunization Program http://www.cdc.gov/vaccines/schedules/index.html	
Sexually transmitted infections: behavioral counseling	Intensive behavioral counseling for all sexually active adolescents and for adults who are at increased risk for STIs	The CDC recommends routinely obtain a sexual history from their patients and encourage risk reduction
Syphilis infection: screening	Persons at increased risk for syphilis infection including MSM and those engaged in high-risk sexual behavior, commercial sex workers, persons who exchange sex for drugs, and those in adult correctional facilities	The CDC recommends universal screening for persons in correctional facilities
TB screening	Recommendation in progress	CDC recommends targeted testing for latent tuberculosis infection (LTBI) in high-risk populations (shelters, migrant farm camps, prisons)

[a]USPSTF A and B Recommendations. US Preventive Services Task Force. December 2014. AHRQ, with permission. http://www.uspreventiveservicestaskforce.org/Page/Name/uspstf-a-and-b-recommendations/

[b]In most cases the AAFP agrees with the USPSTF. Circumstances where there are differences have been noted. Summary of Recommendations for Clinical Preventive Services. November 2014. AAFP, with permission. http://www.aafp.org/dam/AAFP/documents/patient_care/clinical_recommendations/cps-recommendations.pdf

[c]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

[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

outcome expectancy, inertia based on previous practice, and external barriers such as patient and environmental factors [30]. The following sections consider these barriers more fully.

Time constraint: Time constraints affect even the most prevention-oriented providers. Patients 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 contrast, 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. Furthermore, some services may require time-consuming patient education or counseling. Often it is necessary for practices to reevaluate the delegation of duties, shifting some responsibilities to nursing and

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Table 4 Continuation of USPSTF A and B recommendations for adults

Mental health conditions and substance abuse		
Alcohol misuse: screening and behavioral counseling	Screen adults aged 18 years or older for alcohol misuse and provide persons engaged in risky or hazardous drinking with brief behavioral counseling interventions to reduce alcohol misuse. "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?	
Cognitive impairment in older adults (≥65 y/o): screening	Insufficient evidence	Included in Medicare's Annual Wellness Visit benefit (2011). The Alzheimer's Association recommends an algorithm involving a health risk assessment, patient observation, and unstructured questioning (Mini-Cog Test, the General Practitioner Assessment of Cognition)
Counseling and interventions to prevent tobacco use and tobacco-caused disease	Ask all adults about tobacco use and provide tobacco cessation interventions for those who use tobacco products. *The "5-A" framework*: 1. Ask about tobacco use 2. Advise to quit through clear personalized messages 3. Assess willingness to quit 4. Assist to quit 5. Arrange follow-up and support	
Depression in adults: screening	Adults aged 18 and over when staff-assisted depression care supports are in place to assure accurate diagnosis, effective treatment, and follow-up ("Over the past 2 weeks, have you felt down, depressed, or hopeless?" and "Over the past 2 weeks, have you felt little interest or pleasure in doing things?")	
Miscellaneous		
Fall prevention in older adults: counseling and preventive medication	Exercise or physical therapy and vitamin D supplementation to prevent falls in community-dwelling adults aged ≥65 years who are at increased risk for falls	The CDC recommends exercise, home modification for hazard reduction, and multifaceted (including medical screening for visual impairment and medication review)
Osteoporosis: screening, women	DXA in women aged ≥65 years and in younger whose fracture risk is ≥ than 65-year-old white women who have no additional risk factors http://www.shef.ac.uk/FRAX/	
Intimate partner violence screening, women	Screen women of childbearing (18–46) age and provide or refer women who screen positive to intervention services. *HITS*: *Hurt*, *Insult*, *Threaten*, *Scream* Insufficient evidence to recommend screening all elderly or vulnerable adults (physically or mentally dysfunctional) for abuse and neglect	
Recommendations for pregnant women		
Asymptomatic bacteriuria	Urine culture for pregnant women at 12–16 weeks' gestation or at their first prenatal visit, if later	
Breastfeeding: counseling	Interventions during pregnancy and after birth to promote and support breastfeeding	
Chlamydial infection: screening	Pregnant women aged 24 and younger or pregnant women aged 25 and older at increased risk	
Folic acid to prevent 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	
Gestational diabetes mellitus, screening	Asymptomatic pregnant women after 24 weeks of gestation	ACOG: all pregnant women with a patient history or the 50-g OGCT
Hepatitis B (HBV): screening	Pregnant women at their first prenatal visit	
Iron deficiency anemia: screening	Routine screening in asymptomatic pregnant women	

(*continued*)

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Table 4 (continued)

Preeclampsia: low-dose aspirin	Low-dose aspirin (81 mg/day) as preventive medication after 12 weeks of gestation in women who are at high risk for preeclampsia
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.
Syphilis infection in pregnancy	Screen all pregnant women for syphilis infection
Tobacco use in pregnant women	Recommends that clinicians ask all pregnant women about tobacco use and provide augmented, pregnancy-tailored counseling for those who smoke

other staff in order to allow providers to cover the preventive service needs of most patients.[31] It has been estimated that full adherence to USPSTF recommendations could require 7.3 physician hours out of each working day [32].

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. As is evident from the above review, confusion may also stem from updates to guidelines and/or conflicting recommendations from different organizations.

Coding and billing difficulties: Though electronic medical records (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 even introduce new challenges into daily practice. It is often difficult to receive reimbursement for preventive services. While many insurers have long recognized the value of a set of covered preventive items, other indemnity insurance plans and Medicare have traditionally been reluctant to cover common preventive services. It was not until 2005 that most insurers began to recognize the "preventive care visit." It is encouraging to note that the list of covered preventive services grows more comprehensive annually, particularly in light of the Accountable 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. This failure to expand Medicaid means that those states' residents may continue to lack access to preventive coverage [33].

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 in the most efficient way, 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.

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Access and socioeconomic barriers: The greatest barrier to patient adherence is a lack of access to preventive services and primary care in general. A lack of access may stem from patient choice. Cost barriers to regular primary care visits are important, but sociodemographically vulnerable groups are also more likely to face other barriers that include transportation, competing time demands, fear, perceptions of risk, provider time pressures, and fragmented care [34]. These dynamics may result in visits to emergency departments when the situation has become acute. In this scenario, most often the presenting complaint is remedied on a short-term basis, and other preventive services are not likely to be rendered. Even in the primary care office setting, patients may refuse or delay preventive services because of the additional associated costs.

Health literacy: Health literacy is an important factor impacting patient adherence to preventive care across cultural and socioeconomic groups [35]. Low health literacy, low incomes, and low education are often correlated. Lifestyle and behavioral health are key components in many of the leading causes of mortality and morbidity in the USA. Obesity and type 2 diabetes are examples of preventable yet highly prevalent and increasingly common conditions in primary care populations that 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 women's preventive service utilization have identified cultural and racial differences, even among physicians receiving care [36, 37]. 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, previous preventive service or other medical experiences, obesity, and location may all contribute to the likelihood of patient compliance as well [37–39]. 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 [40]. Unfortunately, in many cases, the implementation of such services requires a financial investment by providers on the front end and faces the reimbursement challenges previously discussed.

***Training and time*:** Improvement strategies can produce significant results by targeting a key barrier identified by providers within a particular practice. Readiness-to-change surveys may be helpful in this regard since there is consensus that a systems approach is needed [41]. If, for example, providers report that they lack training about a new guideline or screening tool, then training targeting that particular item may be sufficient. This scenario 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 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 [42]. Nursing staff effort can be utilized to not only deliver 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 [43].

***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

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aforementioned barriers in order to be successful. Practice facilitation, which is in essence the act of 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 [41]. The interest of practices to adhere to guidelines and pursue high standards of care while maintaining the capacity to meet individual patient needs has generated a demand for and a range of practice improvement models.

***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. The PCMH principles were developed by the American Academy of Family Physicians, the American College of Physicians, the American Academy of Pediatrics, and the American Osteopathic Association and 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 [44]. 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 (HIT) utilization, 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 status urban or rural areas, tend to serve populations with a higher incidence of preventable disease, less access to treatment, and lower health literacy. 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, but at the same time, this offers an opportunity for the practice to achieve greater 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 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 be helpful in addressing these issues.

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Family Medicine
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Health Promotion and Wellness

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The evidence shows that health and well-being are affected and created by a combination of physical activity, nutrition, and rest. Family physicians can directly impact all of these components by educating and guiding patients regarding healthy lifestyle choices. With appropriate nutrition, physical activity, and rest, bodily function is optimized, and health and well-being of patients and communities are improved. In addition, tobacco cessation has been shown repeatedly to directly improve morbidity and mortality. While we know that health outcomes are also heavily affected by socio-demographic factors, this chapter is focused on patient lifestyle choices.

Lifestyle Choices and Risk of Disease

Individual and familial risk of disease throughout the lifespan can be modified positively or negatively by lifestyle choices and behavior patterns. Preventable diseases account for 60 % of all non-communicable disease deaths. The main causes of preventable disease and death are related to poor lifestyle choices, especially physical inactivity, unhealthy diet, and tobacco and alcohol abuse [1]. This chapter will focus on tobacco cessation, activity, and nutrition to promote health and well-being in the United States and reduce the burden of preventable disease.

Physical Activity

Regular physical activity (PA) is associated with enhanced health and reduced risk of all-cause mortality [2]. Research shows that a low level of physical activity exposes an individual to a greater risk of dying than does smoking, obesity, hypertension, or high cholesterol. Regular physical activity can [3]:

- Reduce mortality and risk of recurrent breast cancer by approximately 50 %
- Lower the risk of colon cancer by over 60 %
- Reduce the risk of developing Alzheimer's disease by 40 %
- Reduce the incidence of heart disease and high blood pressure by 40 %
- Lower the risk of stroke by 27 %
- Lower the risk of developing type 2 diabetes by 58 %
- Be twice as effective in treating type 2 diabetes than the standard insulin prescription
- Can decrease depression as effectively as Prozac or behavioral therapy
- In an elementary school setting, regular physical activity can decrease discipline incidents involving violence by 59 % and decrease out of school suspensions by 67 %

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Physical Activity Guidelines for Pregnancy

Most studies show the overwhelming benefits of physical activity to the maternal-fetal unit. Physical activity has a role in chronic disease prevention for both mother and offspring [4]. Obesity is the most common chronic disease of pregnancy and affects mother and child negatively [5]. Maternal BMI increases in pregnancy correlate with the odds of an overweight child. Excessive gestational weight is associated with higher likelihood of the child becoming overweight. Exercise during pregnancy reduces the likelihood of excessive weight gain. A vast majority of women who exercise during pregnancy continue to exercise after birth, and parental physical activity correlates positively with the physical activity of their offspring [5].

ACOG recommends that, in the absence of either medical or obstetric complications, pregnant women should exercise at a moderate level for 30 min or more per day on most, if not all, days of the week [4]. Weight-bearing and non-weight-bearing exercises are likely to be safe during pregnancy. However, physically active women with a history of or risk for preterm labor or fetal growth restriction should be advised to reduce her activity in the second and third trimesters [6]. Physical Activity Readiness Medical Examination (PARmed-X) for pregnancy can assist in evaluations of medical problems that may require special considerations in pregnant patients. For a full list of absolute and relative contraindications, see the ACOG statement or the ACSM Exercise Prescription and Testing guidelines [6].

Physical Activity Guidelines for Children and Adolescents

Physical activity declines with age, while time spent in sedentary activities steadily increases [5]. Childrens' physical activity is closely linked to time spent in front of a screen (e.g., television, computer, cellphone). As screen time increases, vigorous activity declines and BMI increases. The American Academy of Pediatrics (AAP) recommends that children have 60 min of vigorous activity per day, which may be accumulated over the course of a day in smaller increments [5]. Activity should be of moderate intensity and include a wide variety of activities – sports, recreation, transportation, chores, work, planned exercise, and school-based physical education classes. These activities should preferably be unstructured and fun.

Age-specific physical activity considerations [5]:

- Infants and Toddlers – Provide opportunities for safe play activity and movement.
- Preschool (4–6 years) – Focus on fun, playful, and safe activities and movement. Encourage activities that emphasize exploration and experimentation, and begin motor learning such as running, kicking, catching, and throwing a ball. Preschoolers can tolerate walking longer distances. Establish walking as a habit and option for transportation.
- Elementary School-Aged Children (6–9 years) – Encourage play to develop motor skills, visual tracking, and balance. Consider organized sports with the focus on enjoyment.
- Middle School-Aged Children (10–12 years) – Encourage play, movement, and sports. Supervised weight training, emphasizing proper technique with small weights and high repetitions may begin. Avoid heavy weights and max lifts. Additionally, certain types of Olympic-style weightlifts should be avoided, including squat lifts, clean and jerk or dead lifts.
- Adolescents – This is a critical age for promotion of lifetime physical activity. Encourage organized sports, other traditional forms of exercise, or exercise with friends and peer group.

Physical Activity Guidelines for Adults

A brief summary of American College of Sports Medicine (ACSM) PA recommendations and Physical Activity Guidelines for Americans is included here: [1, 7].

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Cardiorespiratory Exercise

- Adults should get at least 150 min of moderate-intensity exercise per week.
- Exercise recommendations can be met through 30–60 min of moderate-intensity exercise (5 days per week) or 20–60 min of vigorous-intensity exercise (3 days per week).
- One continuous session and multiple shorter sessions (of at least 10 min) are both acceptable to accumulate desired amounts of daily exercise.
- Gradual progression of exercise time, frequency, and intensity is recommended for best adherence and least injury risk.
- People unable to meet these minimums can still benefit from some activity.

Resistance Exercise

- Adults should train each major muscle group 2 or 3 days each week using a variety of exercises and equipment.

Flexibility Exercise

- Adults should do flexibility exercises at least 2 or 3 days each week to improve range of motion.

Neuromotor Exercise

- Neuromotor exercise (sometimes called "functional fitness training") is recommended for 2 or 3 days per week. Neuromotor exercises develop motor skills. They work a precise group of muscles that are used to perform a learnt act and improve balance, coordination, gait, and agility. Examples of activities that incorporate neuromotor exercises are yoga and thai chi.

Physical Activity Guidelines for Older Adults

The structural and functional decline, overall decrease in physical activity, and increase in chronic disease that accompanies human aging can all be limited by physical activity [8]. Older adults are defined as those older than 65 years or adults between 50 and 64 years who have chronic conditions or functional limitations. Recommendations for older adults are similar to those for adults, with a few special considerations [8]:

- Patients who are deconditioned, functionally limited or with chronic conditions that may affect their ability to be active, should start with low intensity and duration.
- Activities that do not impose excessive orthopedic stress like walking, stationary bike, or aquatic exercise should be considered.
- For flexibility, static stretches are encouraged versus multiple options for others.
- Neuromotor exercises should focus is on progressive balance improvement.

Physical Activity Assessment and Counseling Tools

Many resources are available to family physicians to help incorporate regular counseling into patient visits. These resources and tools should be used in conjunction with behavior change counseling,

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motivational interviewing, and the five A's (Ask, Advise, Assess, Assist, Arrange). The "Five A's" is a convenient approach to physical activity counseling in clinical practice and reviewed in depth later in this chapter.

Physical Activity Assessment and Counseling for Children and Adolescents

Assess what the child AND parents do for physical activity. There is no clinically validated office tool to assess physical activity in children**.** The physical activity vital sign (PAVS) may be used starting at age 13. PACE+ is a validated tool that may be used in adolescents [9].

PAVS for adolescents:

1. How many days in the past week have you participated in physical activity where your heart was beating faster and your breathing was harder than normal?
2. How many days in a typical week do you participate in activity like this?

Other questions used to assess physical activity in younger children:

- How many days of physical education do you participate in at school in a week?
- How many days in a week do you run, bike, swim, or play a sport for 1 h?
- On average, how many hours each day to you spend in front of a screen, either TV or computer, outside of school?

Counsel parents to be role models for their children and involve the whole family in physical activity. Also, parents should limit screen time to 2 h daily.

Physical Activity Assessment and Counseling for Adults

The adult PAVS consists of two questions:

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?

These two screening questions will provide you with a snapshot of whether your patients are meeting the current PA guidelines of 150 min of moderate intensity physical activity each week. By repeating the assessment of PAVS at every clinic visit, you will be able to track changes in their physical activity levels over time.

In addition to PAVS, there are several validated tools that are designed to facilitate physical activity assessment in adults [3, 10]. These tools evaluate readiness to change, self efficacy, medical contraindications, and other aspects of physical activity. They are available online and include the PAAT, PARmed-X, PAR-Q, and RAPA [10]. They vary greatly in length and content and can be utilized based on physician and patient needs. The most comprehensive guide for PA risk assessment is ACSM's Guidelines for Exercise Testing and Prescription [11]. A useful algorithm based on ACSM guidelines is available for free online as part of the Exercise is Medicine – Healthcare Providers' Action Guide [3].

Sedentary Behavior

Sedentary behavior – sitting for long periods of time – as distinct from simple inactivity has been shown to be a health risk in itself. Meeting the guidelines for exercise does not make up for a sedentary lifestyle [8]. High non-exercise physical activity (NEPA) defined as physical activity that is engaged in to

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accomplish daily activities, such as gardening or cleaning, is associated with a number of positive health markers, including more preferable waist circumference, HDL cholesterol, and triglycerides. Additionally the prevalence of metabolic syndrome is lower in those with higher NEPA in non-exercising AND regularly exercising individuals. Lastly, high NEPA has been associated with a lower risk of CVD events and all-cause mortality [12]. It is important to discuss sedentary behavior and encourage more non-exercise physical activity. For example, substituting walking or biking for short car rides, or using a push mower instead of a riding mower can be very helpful. Additionally, these lifestyle activities are more likely to be sustained than structured activities such as exercising in a gym [10].

Exercise Prescription

For most healthy adults, the simplest prescription is to recommend an increase in activity in daily routines to prevent a sedentary lifestyle and to provide a goal of achieving 150 min of moderate intensity physical activity each week. It is important that a written physical activity prescription be provided. Written prescriptions are an effective means of motivating patients to be more physically active [3].

Consider a physical activity referral to a fitness professional if it is felt that additional instruction or structure is needed. Identifying other community programs may help to personalize recommendations. Numerous mobile technologies exist for promoting, tracking, and advancing physical activity. These include apps, websites, and individual devices.

Nutrition

Nutrition is the intake, digestion, and absorption of nutrients that provide energy and determine the structure and metabolic functions of the human body. With proper nutrition, the body and mind are more resilient and able to develop, respond, and adapt to the environment. The challenge for family physicians has been to determine which of the various nutrition recommendations are appropriate to guide patients to promote health and well-being. This section is focused on evidence-based nutrition counseling for the general population with the goals of promoting health and well-being.

Low fat diets have failed a large portion of the US population. By decreasing the high density caloric intake of fats in the American diet, it was assumed that daily caloric intake would decrease. However, since the initiation of the “low fat” dietary recommendations, the explosion of overweight and obesity, metabolic syndrome, Type II diabetes, sleep apnea, and other weight-related health issues have sky-rocketed to levels never seen before. Individual caloric intake was not decreased by cutting fat, instead the *proportion* of calories changed to a diet with higher intake of calories from sugar [13] and other refined carbohydrates.

Unlike fat, which is satiating, consuming excessive sugar stimulates appetite, triggers cravings for more sugar, and promotes the development of central obesity and insulin resistance. With excessive circulating insulin, the body continues to produce and enlarge ever more adipose cells, mainly around the waist. To maintain this metabolically active excess adipose tissue, once again, the appetite is stimulated to support energy needs. This vicious cycle accelerates as insulin resistance develops further.

One promising approach to improving health with nutrition is the Mediterranean style diet, which is similar to diets found in the areas of the world where more people experience longevity and healthy aging [14]. These diets are not exactly defined but consist of mainly plant-based foods including vegetables, fruit and nuts, whole grains and legumes, moderate poultry and fish, olive oil in place of butter, margarine or cream, reduced simple carbohydrates, and minimal red meat and processed foods [15].

Greater adherence to Mediterranean style diets have been shown to reduce cardiovascular mortality [16]; decrease risk of cancer incidence and mortality [17]; decrease risk of cerebrovascular disease [18]

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and the metabolic syndrome [19]; and reduce cognitive decline and dementia [20] with aging. In fact, greater adherence to the Mediterranean style diet has been found to result in longer leukocyte telomere lengths which have been linked to healthy aging and longevity [21, 22].

Some tools to assess dietary quality include food frequency questionnaires (these are fast, inexpensive, and easy to use), 1–7 day food logs (these are more accurate, but require patients prepare ahead of appointment. This may be easier with smartphone apps like MyFitnessPal), and 24 h dietary recall (quick interview during office visit). There is a validated 14 point screening tool to assess adherence to Mediterranean style diet [15]. Also, the simple act of requesting a food log improves eating behavior(s) by developing a greater awareness of what is consumed. Logging food and drink intake can be done easily with smartphone apps and online resources. These can also be used to log physical activity and sleep.

Using a nutrition assessment tool, family physicians or staff can counsel patients appropriately towards a Mediterranean style diet by offering one or two dietary recommendations at a time.

1. Limit sugar: Work towards limiting or eliminating sweetened food and drink in the diet. Recommend avoidance of sugar sweetened beverages. Educate patients that 100 % fruit juice is NOT equivalent to a serving of fruit.
2. Fluids: Most liquids should consist of water, unsweetened tea, coffee, dairy or dairy alternative with calcium. Wine (up to one glass for women and up to two glasses for men) may be included as appropriate.
3. Vegetables: Work towards daily consumption of leafy greens and increased quantity and variety of colors of vegetables to ensure adequate supply of the various nutrients and phytochemicals necessary for disease prevention and health promotion [23].
4. Grains: Suggest replacement of processed grains with whole grains. Grain may be replaced entirely with more vegetables. This strategy improves insulin resistance, blood sugar control, and triglyceride levels [24, 25].
5. Protein: Include plant-based protein sources (nuts and legumes) and animal protein sources such as eggs, seafood, poultry, and wild game. Limit commercially raised red meat.
6. Fats: Recommend avoiding trans-fatty acids and switching to naturally occurring fats and olive oil.
7. Probiotics can be recommended for health promoting benefits [26].
8. Non-nutritive sweeteners: Despite much controversy, there are no clear evidence that these FDA-approved sweeteners are harmful. There are acceptable daily intake (ADI) levels for each of the seven FDA-approved non-nutritive sweeteners (acesulfame K, aspartame, neotame, saccharin, sucralose; and food products such as luo han guo fruit extract, stevia) [27].
9. Individual patients have different needs. Referral to a registered dietician is recommended for patients with complicated medical issues or needs. For example, the Dietary Approach to Stop Hypertension (DASH) diet may benefit those with hypertension and lower carbohydrate diets may benefit those with metabolic syndrome or type II diabetes. This diet has been found to be more effective than low fat diets in reducing cardiovascular risk factors [28].
10. Recommend sitting down to eat meals and connecting with others. Regular relaxing breaks spaced throughout the day improve well-being [29].

Evidence and Common Areas of Concern

Fats

Trans-fats are primarily found in artificially hydrogenated fats such as margarine and shortening and should be avoided due to adverse effects on lipid panels and cardiovascular health. Rather than decreasing

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saturated fat in the diet, modification of dietary fat leads to cardiovascular benefit [30]. Recommend switching fats from red meats and sugar-laden foods to fats from fish, avocado, nuts, and nut oils (i.e., coconut or olive oil).

Fiber

Dietary fiber is found in whole grains, vegetables, legumes, and fruit. Dietary fiber from grains, vegetables, and legumes is inversely related to deaths from cardiovascular disease, cancer, infectious and respiratory disease in both men and women. This is not true for fruit fiber however. Encouraging high fiber food choices may reduce the risk of premature death [31]. There is no upper limit of recommended fiber intake, although as a practical matter, excess intestinal gas may be experienced by those who increase their fiber intake quickly. The recommended total daily fiber intake is 14 g fiber per 1000 kcal ingested [32].

Sodium

According to the Institute of Medicine, evidence supporting the recommendations for strictly limiting dietary sodium seems to be weak or nonexistent for many medical issues [33]. While there is some evidence that salt restriction may lead to increased insulin resistance and cardiovascular mortality [34], the data are conflicting. There are also data that suggest that the risk of death and cardiovascular events are lower when sodium consumption is maintained between 3–6 g daily [35].

Calcium and Vitamin D

There exists an inverse association between 25-hydroxyvitamin D levels and all cause mortality in primary prevention cohort studies. Vitamin D3 supplementation (but not Vitamin D2) reduced all cause mortality by 11 % [36]. There is inconsistent evidence to support vitamin D and calcium supplementation for improved health outcomes related to pregnancy, bone or cardiovascular health, incidence of cancer, immune function, all-cause mortality or vitamin D status in the general population [37].

Multivitamins

Links between vitamin supplementation and cardiovascular disease are also complex. Multivitamins alone have not consistently been shown to improve cardiovascular outcomes or to reduce mortality risk. The United States Preventive Services Task Force (USPSTF) recommends against the use of beta carotene or Vitamin E supplementation for primary prevention of cardiovascular disease or cancer [38, 39].

Fish Oil

No trials examining fish oil with endpoints of vascular events or mortality were identified. Clinically significant lower triglyceride levels and VLDL were noted in trials with mean omega-3 poly-unsaturated fatty acid (PUFA) doses of 3.5 g/day. No significant changes in total or HDL cholesterol, HbA1c, fasting glucose, fasting insulin, or body weight were observed. No adverse effects of the intervention were reported [40].

Iron

Iron deficiency is the most common nutritional deficiency and leading cause of anemia in the USA and the world. People at high risk for iron deficiency anemia include infants and children after 6 months old, unless they are breast feeding or drinking iron fortified formula, people who restrict some food groups from their diets, women with heavy menstrual periods, and pregnant or breastfeeding women. Among children with iron deficiency, decreased motor and brain development as well as poor health and even death can be prevented with appropriate iron supplementation and education to avoid overconsumption of cow's milk, which limits iron absorption.

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Nutrition Recommendations for Special Populations

Vegan

Vegans do not consume any animal products and are at risk of developing Vitamin B12 deficiency. Counseling about Vitamin B12 supplements or fortified cereals or beverages is needed. Consultation with a registered dietician should be considered.

Vegetarian

When planned well, vegetarian diets may provide complete nutrition for individuals of all ages. Vegetarian patients may want to ensure adequate calcium, iron, zinc, and vitamins D and B12 with the guidance of a registered dietician. Vegetarian meal planning assistance is also available through the American Dietetic Association at http://www.eatright.org/.

Pediatrics

Water and dairy or dairy equivalent containing calcium and vitamin D are the only beverages children need. For children under 2 years old, dietary fat should not be restricted. Recommend introducing and re-introducing a variety of colorful vegetables, proteins, whole grains, and whole fruit to picky eaters as their tastes are constantly developing. Minimizing or eliminating sugar sweetened beverages and foods will help prevent obesity.

Geriatrics

Older adults require adequate protein combined with physical activity to limit sarcopenia which can **increase** frailty and contribute to the development of metabolic disorders [41].

Mind-Body Connection and Resiliency

The mind-body connection to health and healthcare costs is well established. Stress, poor lifestyle choices, and disease symptoms often coexist and if not managed, exacerbate each other. Mind-body therapies act through the common factor of increasing nitric oxide which elicits the relaxation response (RR) and stimulates the body's endogenous stress management responses. These include adaptive changes to gene expression and neurobiological signaling that seem to promote health and resiliency [29]. The RR effectively treats stress and reduces symptom severity in chronic disease, increases positive lifestyle behaviors, and improves many mental health symptoms [42]. The RR has been described as a hypo-metabolic state with decreased sympathetic tone, [29] resulting in lower heart rate, blood pressure, respiratory rate, and oxygen consumption and increased heart rate variability. At the cellular level, the RR positively affects gene expression related to mitochondrial metabolism, insulin secretion, telomere maintenance, and inflammatory pathways [43]. Of the multiple mind-body techniques that elicit the RR, meditation, yoga, and tai chi are reviewed below.

Meditation, tai chi, yoga, and sleep are some of the ways to obtain the health benefits of stress reduction by inducing the relaxation response. Meditation has repeatedly been shown to be effective in decreasing stress in otherwise healthy individuals [44–46]. Mindfulness meditation has been shown to result in positive changes in the brain and immune function [47]. There is evidence that mindfulness meditation programs may alleviate anxiety, depression, and pain, and they may reduce stress, distress, and improve quality of life in those patients with chronic disease or mental health diseases [29, 45,

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46]. Also, in the pediatric population, among children 6–18 years old, sitting meditation was effective in improving physiologic (improved systolic blood pressure, cardiac output, urinary sodium excretion, and endothelial vasodilation function) parameters, as well as psychosocial and behavioral conditions [48].

Mind-body movement programs such as tai chi and yoga appear to have physiological and psychosocial benefits [49, 50]. Tai chi has been shown to promote balance control, flexibility, and cardiovascular fitness in older patients with chronic conditions [50]. In addition, adequate sleep is essential to rest and resiliency. Inadequate sleep leads to a range of health problems and is addressed elsewhere in this text.

Identifying Disease Risks: Weight, Waist Circumference and Body Mass Index (BMI) Screening

Regular physical activity levels, weight, waist circumference, and BMI can be objective measures of overall health risk over time. In addition to physical activity assessment, patients of all ages can be screened for overall health risk assessment with simple measures of height, weight, and waist circumference. Using height and weight, BMI can be calculated to screen for underweight, overweight, and obesity which are linked with increased risks for adverse health outcomes in all ages [51].

Body mass index (BMI) is calculated as weight (kg)/height^2 (m^2). Abnormal BMI, excessive weight loss, or weight gain at any age can be associated with negative health outcomes at all ages. Excess weight is a risk factor for many types of cancer.

Definitions of underweight, overweight, and obesity depend on BMI and differ in pediatrics and adults. In children, BMI *percentiles* are used for assessment from 2 years old and older: these are based on the age and sex of the child. Underweight is defined as those with a BMI $<$5th percentile, overweight, as having a BMI between the 85–95 percentiles, and obesity as a BMI $>$95th percentile for age and sex [52]. In adults, the definitions are based on weight and height. Underweight is considered to be a BMI $<$18.5, the BMI classified as overweight is between 25 and 29.9 and obesity is a BMI greater than 30, with morbid obesity defined as a BMI $\geq$40. In postmenopausal women and older adults, being overweight is less strongly correlated with mortality than it is in younger age groups [53].

An equally important risk factor assessment in adults is the waist circumference. Although the traditional measurements were defined as men $>$40 in. (102 cm) or women $>$35 in. (88 cm), it is now recognized that different ethnic groups have different waist circumference measurements at which elevated cardiometabolic risk occurs. The waist circumference is measured using a tape at the level of the top of the iliac crest.

Monitoring a patient's weight, BMI, and waist circumference is a relatively simple way of monitoring for increased disease risks in the outpatient office. In the pediatric population, the child's weight and BMI percentile is expected to follow a similar curve if he/she is getting adequate nutrition and growing appropriately. Appropriate weight assessment and management at all ages is important in optimizing health.

In pediatrics, the height and weight should be measured and monitored for unhealthy trends during every routine pediatric wellness visit with specific screening for risk of overweight and obesity beginning at 2 years old [52]. Though specific screening frequency guidelines do not exist for adults, it is recommended to obtain a waist circumference and BMI at routine chronic disease follow up visits and/or during annual exams in order to recognize unhealthy weight trends and to provide earlier interventions that may be more effective in promoting health.

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Tobacco Cessation

Tobacco use is a modifiable risk factor responsible for disease and deaths from cancer and cardiovascular and pulmonary diseases. There is no evidence that any form of tobacco use is safe. Cessation should be addressed with all patients who use tobacco in any form [54]. The "Five A's" framework was developed to allow physicians to incorporate smoking cessation counseling into practice [54]. It is described below.

There are medication and non-medication options to assist patients with smoking cessation. Medication options include nicotine replacement, varenicline, and buproprion [54]. Nicotine replacements (gum, inhaler, lozenge, patch, nasal spray) increase the chances of quitting successfully by 50–70 %. They usually need to be titrated based on the amount the patient smokes. Varenicline is a nicotine receptor agonist. It reduces cravings and withdrawal symptoms while blocking the binding of smoked nicotine. It increases the chances of quitting by two- to threefold. Buproprion doubles the odds of smoking cessation when compared to placebo.

Non-medication options include complementary and alternative therapies including acupuncture and hypnotherapy which are not supported by evidence. Exercise is useful and literature supports the use of internet-based interventions and telephone quit lines [54].

E-cigarettes were introduced in the United States in 2007. These operate with a small heating element that creates a water vapor that can be inhaled. There are still many concerns regarding their use and at this time, their safety is unknown [55].

Promoting Adoption of Healthy Behaviors

In order to have a successful intervention in a busy office practice, it is important to be aware of evidence-based treatment options and then to have an effective and practical method to facilitate behavior change, improve treatment compliance, and support successful adoption of healthy lifestyle choices.

Understanding that many patients already have ideas about what they "should be doing" for health, and that patients will only respond to information and suggestions for which they are ready, physicians will be more effective in promoting healthy behavior changes using the "Stages of Change (SOC)," model and appreciate that the patient must progress through each stage *in sequence* to be successful. Two tools that family physicians can use to facilitate this progress include motivational interviewing (MI) [56] and the 5 A's [57] (see Table 1).

5 A's

The Five A's construct – Assess, Advise, Agree, Assist, and Arrange, adapted from tobacco cessation interventions in clinical care – provides a structured strategy for many different types of behavioral counseling intervention [57].

Ask – Address the behavior change agenda
Advise – Provide personalized information on benefits of change
Assess – Address previous attempts, and identify barriers and readiness for change
Assist – Strategize to overcome barriers, and match advice to stage of change
Arrange – Arrange follow-up, and inquire about behavior and readiness for change
Agree* – Shared decision making with a plan that physician and patient mutually agree upon

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Table 1 Counseling for behavior change incorporating Stages of Change and Motivational Interviewing (Adapted from [56, 59])

Stages of change	Patient status	Physician action: motivational interviewing
Precontemplation	No interest, unaware	Assess awareness, help develop awareness, plant the seed, offer hope
Contemplation	Longest stage Aware of risk. Ambivalent: wants to change "but" may not believe it is possible or may not know how	**Identify ambivalence** ("I should start exercising *but* I have no time.") **Listen for change talk**: **Desire** ("I wish I ate healthier," "I want to start exercising.") **Ability** ("I could eat healthier if. . .," "I might be able to start exercising if. . .") **Reasons** ("I would probably feel better if I started eating healthier," "I want to be able to run around with my grandkids.") **Need** ("I should plan ahead and make my lunches," "I have to find a place to walk during lunch.") **Commitment** ("I am going to take a 10 min walk three times a week," "I plan to bring my lunch to work every day.") **Taking steps** ("Last week, I brought my own lunch 4 days, and I started walking with a coworker during lunch on those days.") **Help patient progress in his/her discussion** **Ask permission** ("Would you like to talk about quitting smoking?) **Offer choices** ("We can discuss some of the ways to quit smoking: "cold turkey," nicotine patches, nicotine gum, or medications.") **Share others' success stories** that the patient will be able to identify with and visualize for him/herself
Preparation	Change planned within next 6 months Patient hopeful and inspired	Continue to encourage change talk ("I could eat a salad for lunch most days") Focus on eliciting patient's positive consequences after change ("I could go on a cruise with the money I save if I quit smoking.")
Action	Change made within past 6 months Resisting return to old habits	Elicit patient's sense of satisfaction and pride ("My clothes fit better and my friends are asking me what I am doing!") Provide recognition and positive support ("You must feel so proud of your success.")
Maintenance	Avoid triggers	Positive reinforcement. Enthusiasm. Watch for signs of relapse

*Some models omit "Ask" and incorporate that information in "Assess." Agree is then added as the fifth "A."

A successful visit means moving forward through the SOC in the appropriate sequence, not necessarily immediately adopting the new lifestyle habit. The physician can use brief moments through multiple visits to help the patients' progress through predictable stages and toward the ultimate desired behavior change [57, 58, 59] (see Table 1).

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Patient health and well-being are strongly impacted by healthy lifestyle choices, including avoidance of tobacco, increased physical activity, improved nutrition, and adequate rest. By counseling and encouraging patients and their families and advocating for tobacco control and other measures to improve health, physicians can have large-scale impacts on populations and improve both individual and public health outcomes.

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Health Care of the International Traveler

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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 is set to exceed 1.1 billion by the end of 2014 [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].

Pretrip Consultation

A pretrip consultation is recommended at least 4–6 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 and heart disease 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.

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

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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 two-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 <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 is 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 three-dose series called Twinrix, in which 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 <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) and potential for sexual contact. An injury or illness while abroad which leads to local medical care may also increase risk of exposure to hepatitis B. Traveler risk factors should be assessed prior to administration of hepatitis B vaccination.

Hepatitis B vaccine exists in a three-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 30–55 % immunity, two doses 75 % immunity, and three doses >95 % immunity in adults [4]. At least two 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.

Typhoid

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

There are currently two licensed vaccines in the United States. Typhim Vi is a polysaccharide subunit vaccine, 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 one capsule to be taken an hour before eating every 48 h for four 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

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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 has recently stated that a single yellow fever immunization confers lifelong immunity, but many countries still require a booster every 10 years [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 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 ten 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 travelers to such countries should verify requirements for entry and exit with the CDC's regularly updated recommendations [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.

Our practice is to consider vaccination for all travelers to any country which contains part of the meningitis belt if their travel will extend within a month of the December-June window. Quadrivalent vaccines are recommended. Conjugated vaccine (MCV4) has greater longevity and efficacy so this should be chosen if possible, although only the polysaccharide vaccine (MPSV4) is licensed for use in those over 55. Boosters are required every 5 years should the traveler remain at risk. For those traveling with children under 2 years of age, current vaccination schedules should be reviewed, as they vary by product. Adolescents and preadolescents already vaccinated will not need additional boosters for travel.

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Japanese Encephalitis

Japanese encephalitis (JE) is a mosquito-borne illness prevalent in areas of Asia. Its overall prevalence is one 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 two-dose vaccination, with doses separated by 28 days with the second dose recommended 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 in use for 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. 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 postexposure in these locales. Vaccination can also be considered for travelers who plan on visiting rabies-endemic locations for extended periods of time (>1 month). Vaccination is often quite expensive and consists of a three-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.

Postexposure treatment is three pronged [12], consisting of wound care, administration of the rabies immunoglobulin (if no preexposure 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 one 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

Table 1 Postexposure treatment of rabies [12]

Received preexposure vaccination?	Wound cleansing needed?	Rabies immunoglobulin administration needed?	Postexposure immunization schedule
Yes	Yes	No	Days 0 and 3
No	Yes	Yes	Days 0, 3, 7, 14

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Table 2 Treatment regimens for traveler's diarrhea

	Southeast Asia, including India	Central and South America, Africa, the Middle East
Adults	Azithromycin, 500 mg PO BID × 3 days or 1 g once	Ciprofloxacin, 500 mg PO BID × 3 days
Children <18 years old	Azithromycin, 10 mg/kg once per day × 3 days	Azithromycin, 10 mg/kg once per day × 3 days
Pregnant women (all trimesters)	Azithromycin, 500 mg PO BID × 3 days or 1 g once (category B in pregnancy)	Azithromycin, 500 mg PO BID × 3 days or 1 g once (category B in pregnancy)

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*.

Treatment for traveler's diarrhea is guided by pathogen and location (see Table 2). Ciprofloxacin is the most common antibiotic used to treat traveler's diarrhea in adults and is very effective in all locations in developing countries excluding Southeast Asia [14]. Due to emerging ciprofloxacin resistance and increased rates of *Campylobacter* in Southeast Asia and India, azithromycin is the preferred drug for traveler's diarrhea treatment in this region of the world [14]. 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 [15]. A recent meta-analysis of traveler's diarrhea in several communities around the world showed increased likelihood of clinical cure at 24 and 48 h if combination loperamide/antibiotic therapy is given [15].

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 which 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 which 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. 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 2013 an estimated 128 million cases of malaria with 584,000 deaths, most of which are in children in sub-Saharan Africa [16]. Malaria in travelers is potentially lethal, but avoidable. Each year, there are between 1,200 and 2,000 cases reported in the United States [17].

Four species, *Plasmodium falciparum*, *P. ovale*, *P. malariae*, and *P. vivax*, cause human disease. A fifth species, *Plasmodium knowlesi*, a primate species, causes significant human disease in Southeast Asia, with a dozen cases reported in travelers through 2013 [18]. While all species contribute to human morbidity, the burden of mortality is due to *P. falciparum.* While resistance patterns vary, in general,

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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 <8 years of age and in pregnant and lactating women. Dairy products should be avoided for a 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 not officially indicated for malaria prophylaxis, outside of the practice of presumptive anti-relapse treatment (PART), also known as "terminal prophylaxis." Terminal prophylaxis 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. However, it is active against all forms of malaria and easily tolerated as primary prophylaxis, at the same dosage as used for terminal prophylaxis. Like atovaquone/proguanil, it is started just prior to travel and taken daily, but it is only necessary for 5 days after leaving the malarious area. When used as primary prophylaxis, no terminal prophylaxis is necessary. Primaquine triggers a

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hemolysis in those with G6PD deficiency, so the level of the enzyme should be tested prior to prescribing this drug. Primaquine should not be prescribed 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 diseases, such as Japanese encephalitis, are preventable by vaccination, but the cost and availability of vaccines may discourage their use, especially in short-term travelers. In addition, diseases such as dengue and chikungunya have no treatment or vaccine yet available, so protective measures are the only prevention.

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].

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

A discussion of altitude prophylaxis is recommended for destinations exceeding 2,500 m [22]. The most widely accepted preventive measure is slow ascent [22]. 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 the day prior to ascent and to continue until the traveler has acclimatized at their maximum altitude (generally 48 h) [22]. Acetazolamide can cause side effects such as diuresis and paresthesias 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 [22]. The most effective treatment for altitude illness is descent.

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Safety and Accident Prevention

A significant proportion of the pretravel visit is dedicated toward the discussion of pretrip immunizations, malaria, and traveler's diarrhea. However, the primary cause of death among travelers is accidents, such as motor vehicle accidents and falls [23]. For this reason, the topic of safety and accident prevention deserves specific mention during the pretrip 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 pretrip 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.

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 greater than 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 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 [24].

The most critical subgroup 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 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 [25], and the risk of mortality from this pathogen 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 is the most frequently encountered fever from the Indian subcontinent [26]. 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

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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 which may have failed as a prophylactic agent. Availability of Coartem, however, may be a factor. Parenteral options such as artesunate are effective but should be done in consultation with the CDC. Quinine has a long track record, but its potential for arrhythmias limits its utility.

GI Illness in Returned Traveler

GI illness is one of the most common illnesses in the returned traveler [23]. 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 pretrip consultation section of this chapter.

Diarrheal symptoms lasting more than 2 weeks should prompt screening for *Giardia* and other parasites. Multiple stool samples for O and P testing may need to be submitted to accurately diagnose parasitic infection. The authors recommend three stool O and P samples on three different days, as one 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 post-infectious irritable bowel syndrome (IBS), a diagnosis of exclusion in travelers with prolonged diarrheal symptoms >30 days after travel [27]. The incidence of post-infectious IBS is variable and ranges from 4 % to 31 % across all studies [27]. In one study of North American travelers to Mexico, the incidence was 11 % of all travelers with diarrhea, 10 % of these 11 % being newly diagnosed cases of IBS [28]. 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 [28].

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 value in a returned traveler is eosinophilia. A cutoff of 500×10^6 should be used to promote further evaluation. The most common causes of eosinophilia in travelers are schistosomiasis, filariasis, and nematode infections [29], 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 health-care settings or frequent face-to-face contact with persons residing in a TB endemic location, a PPD screen is recommended 8 weeks after return [30].

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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 [31]. 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 [31]. 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.

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 posttraumatic stress disorder (PTSD) should be considered for all long-term returned travelers when seen by their primary care providers. Counseling is highly recommended for travelers with psychological concerns on reentry.

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Family Medicine
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Preconception Care

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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 2010, the US infant mortality rate was 6.1 per 1000 live births. Despite leading the world in health-care expenditures, the USA ranks 26th among developed nations in infant mortality [3]. Since 2000, after 40 years of improvement, infant mortality rates have stalled and maternal morbidity and mortality are *increasing* [4, 5].

The most important causes linked to infant mortality are preterm birth and birth defects (see Figs. 1 and 2). Birth defects account for 20 % of all infant deaths and affect 1 in 33 infants born in the USA [6]. Approximately 36.5 % of all infant deaths in the USA are attributable to prematurity [7]. 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 [8].

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 heart begins as early as 3 weeks post-conception, and 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 [9]. Unfortunately, approximately 50 % of pregnancies in the USA are unintended, thus limiting the ability to "plan" preconception risk reduction [10]. Unintended pregnancy is an independent risk factor for poor birth outcomes. Additional examples of maternal risk factors which determine birth outcomes are: inter-pregnancy interval, maternal age, exposure to teratogenic

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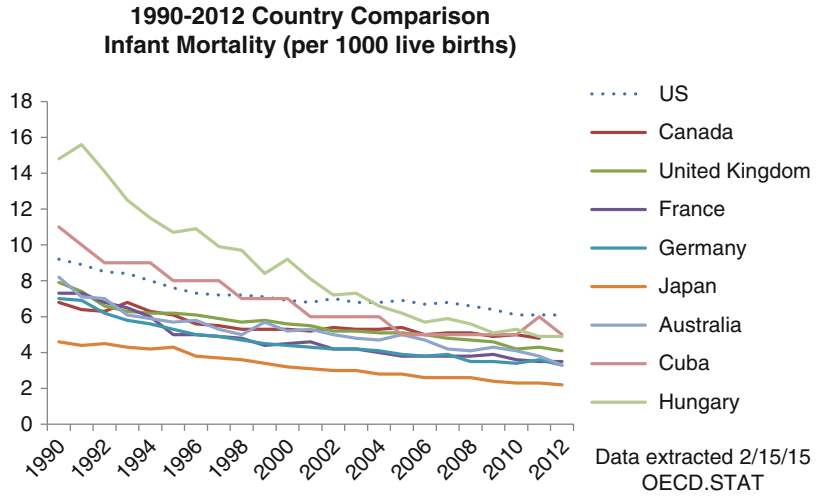

Fig. 1 1990–2012 Country comparison infant mortality (per 1000 live births)

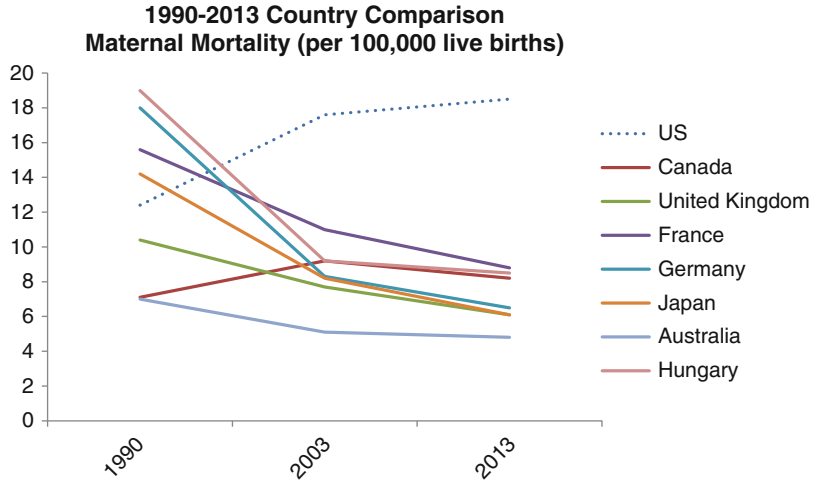

Fig. 2 1990–2013 Country comparison maternal mortality (per 100,000 live births)

medications, exposure to substances, chronic disease control, and preventable congenital anomalies [11] (Table 1).

CDC Recommendations on Preconception Health

In 2006, the CDC released "Recommendations to Improve Preconception Health and Health Care – United States: A Report of the CDC/ATSDR Preconception Care Work Group and the Select Panel on Preconception Care" [1]. This report included 10 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 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

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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 [11]

		Age group (yrs)				Race/ethnicity[a]			
Preconception measure		Total	18–24	25–34	35–44	White	Black	Others	Hispanic
Health care	Insurance coverage[b]	74.9	62	79.8	84.6	81.9	76	82.9	50.3
	Preconception counselling[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 contraception[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)

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 Health Care (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.

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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 10 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 health care 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]. 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" Sanford and Hobbins [19]. 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.

Clinical Content of Preconception Care

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 1). It is essential that these chronic conditions be recognized and treated in the preconception period. For example, poorly controlled or undiagnosed diabetes resulting in hyperglycemia in the first trimester results in a fourfold increase in congenital heart defects and increased risk of pregnancy loss [20].

Previous Obstetrical History

Women who have had three or more spontaneous abortions should undergo additional testing to rule out thrombophilia, thyroid dysfunction, and other potential genetic syndromes. Women with a history of a

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spontaneous preterm delivery are at increased risk of this outcome in the next pregnancy [21]. Women with a prior history of preeclampsia, gestational diabetes, or other poor birth outcomes should prompt additional evaluation for chronic medical conditions and counseling on the importance of early prenatal care.

Family History

A three-generation family history will identify women who are at increased risk for genetic syndromes such as thrombophilia, coagulopathies, hemoglobinopathies, cystic fibrosis, trisomies, etc. 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 [22].

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 [23]. It is important to screen for exposure to violence routinely in the office setting. The CDC has extensive resources at 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 nonpregnancy reproductive-aged women were smoking in 2009 [11]. Approximately 54 % of nonpregnant women of childbearing age consume alcohol and approximately 15.2 % binge drink [11]. 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.

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 [11]. Women using illicit drugs have a higher incidence of medical, psychiatric, psychosocial, and infectious comorbidities.

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 [24]. 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 http://otispregnancy.org/otis_fact_sheets.asp.

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 [25].

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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 18.5 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 [26].

It is important to ask patients about their use of dietary and nutritional supplements. It has been estimated that 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 [24].

Standard Nutritional Recommendations
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 urogenital congenital birth defects [26]. 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 [27].

Vaccine Preventable Infections
Women of reproductive age should be counseled about vaccine preventable infections and offered appropriate immunizations according to the CDC ACIP recommendations [28, 29]. Particularly important for preconception health are: hepatitis B, rubella, varicella, annual influenza, and HPV (for those aged 11–26 years).

Sexually Transmitted Infections
Obtain risk-based STI tests for gonorrhea, chlamydia, HIV, and syphilis.

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.

Preconception Care for Women with Chronic Medical Conditions

Family physicians are well versed to provide preconception care to women of childbearing age because of their expertise in managing a wide range of primary care conditions. However, they must be prepared to understand how the care of these conditions must be adjusted in the preconception period in preparation for the critical period of embryogenesis during the first trimester of an ensuing pregnancy [20, 30]. Table 2 provides an overview of condition and medication management in anticipation of pregnancy for 10 common chronic conditions. It also addresses family planning considerations. Another key information source to

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Table 2 Preconception care of women with chronic medical conditions [20, 30]

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	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	Avoid use of ACEs, ARBs, and spironolactone in pregnancy

(*continued*)

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Table 2 (continued)

Condition	Epidemiology/natural history	Preconception interventions	Contraception strategies	Medication use
	adverse outcomes if they have HTN		progesterone-only or barrier methods	
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	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

(*continued*)

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Table 2 (continued)

Condition	Epidemiology/natural history	Preconception interventions	Contraception strategies	Medication use
		pregnancy; recommend MFM consultation		
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 [31]	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 [32]
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

assist women is http://www.cdc.gov/reproductivehealth/UnintendedPregnancy/Contraception_Guidance.htm.

Preconception Risk Assessment

At the conclusion of a preconception visit, the clinician summarizes the significant risk factors that were identified in the process of screening for positive family history, prior obstetrical history, psychosocial factors, alcohol, smoking, illicit drug use, medication use, and presence of active medical conditions that

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should be addressed that will have a beneficial effect on the woman's current health and future pregnancy outcome. The clinician will then recommend a specific action plan to address the identified risk factors. In many circumstances the development of the preconception risk assessment and action plan may occur over two visits.

Strategies for the Prevention of Adverse Birth Outcomes

Because 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 health-care 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 account 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 health-care providers and patients with developing a reproductive life plan which can be accessed at http://www.cdc.gov/preconception/rlptool.html.

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 [33].
- *One Key Question® Initiative* (Oregon Foundation for Reproductive Health) – This initiative 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

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which reproductive needs and preferences are explored. Women are then offered essential preventive services based on identified needs [34] (http://www.onekeyquestion.org).

- *The North Carolina Statewide Multivitamin Distribution Program* – This program provides multivitamins with folic acid to low-income, nonpregnant 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 [35] (http://everywomannc.com/public-health-programs/north-carolina-programs/statewide-multivitamin-distribution-program).
- *The IMPLICIT Network* – This collaborative of 19 family medicine residency programs 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 family physicians are trained in best practices (www.fmec.net/implicitnetwork.htm).
- *Nurse-Family Partnership* – This program partners low-income, first-time mothers with a registered nurse early in pregnancy; 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 Health Care Initiative encourages women of childbearing age to maintain good health, reduce health risks, and make intentional decisions about pregnancy (www.cdc.gov/preconception/showyourlove).

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 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

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lifestyle, follow treatment plans for chronic conditions, and take responsible steps to ensure planned, appropriately spaced pregnancies [36].

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 Health Care – 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 (http://www.cdc.gov/preconception/hcp/index.html).
- The National Preconception Curriculum and Resource Guide for Clinicians developed by the Preconception Health and Health Care Initiative – includes the National Preconception/Interconception Care Clinical Toolkit and online continuing education modules (http://beforeandbeyond.org).
- National Healthy Start – HRSA-funded, locally administered programs that connect pregnant women and new mothers in at-risk communities with health-care 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 (http://www.marchofdimes.org/professionals.aspx).

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Normal Pregnancy, Labor, and Delivery

Naureen B. Rafiq

Contents

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 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 Ballantynes' methods, began applying these principles to slum dwellers in New York

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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 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 providing 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 the 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 exam to counsel on healthy lifestyle, identifying social, behavioral, environmental, and biomedical risks that can affect fertility or pregnancy outcomes. Although many women will seek prepregnancy 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.

Woman's work, home, pets, hobbies, potential toxic exposures, nutrition, hygiene, chronic diseases, teratogenic medications, and substance abuse are 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 [7].

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.

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. It 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 a 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 are not dehydrated.

Patients may have vaginal bleeding or spotting around the time of their usual menstrual cycle likely due to implantation of embryo in the uterine wall that completely resolves on its own. 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 – 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 in the first trimester and may go on into the second and third trimester. It is thought that progesterone may have a role in inducing sleep (reference needed). Rest and adequate intake of protein may be helpful.

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

Pregnancy causes dilation of blood vessels that leads to drops in blood pressure, which may cause 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.

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 of it, 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 25–35lb (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 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. This helps to prevent maternal pertussis infection and also provides the fetus with some level of immunoglobulin protection against pertussis after birth.

   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 [8]. 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 [9].

    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 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, [10, 11] history of domestic abuse, and substance abuse (Table 1).

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 [12–14].

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 24th 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 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. Hormone

Table 1 Common screening tests in pregnancy

First trimester
Complete blood count
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
1h 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

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 [15].

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. If the discharge is foul-smelling, green or yellow, bloody, or if there is a lot of clear discharge, then other etiologies may be explored.

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 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. All 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 the 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. The cell free fetal DNA gets fragmented and gets into maternal bloodstream via shedding of placental microparticles. It can be detected as early as 7 weeks of gestation, and its 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 although carries no risk of miscarriage 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 the confirmatory test that measures amniotic fluid level as well as the 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. Twenty-week uterus is up to the umbilicus and the fundal height usually corresponds in centimeters with the week of gestation and is 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 for detection of any developmental abnormalities.

Third Trimester

The third trimester is from 25 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 4–4 ½ lbs (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 5 ¾ lbs to 6 ¾ lbs (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 6 ¾ lbs to 10 lbs (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 pounds (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. A constant low level of energy can be a sign of anemia and should be ruled out.

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 avoid 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.

Growing uterus puts pressure on the bladder most heavily in the third trimester leading to frequency of urination and sometimes urges incontinence. Trying to urinate on a schedule, such as every hour or two helps prevent this. It is also important to drink eight-ounce glasses of water a day 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 put feet up 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 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-hour 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 for reasons unknown in nonwhite races including black, Hispanic, American Indian, and Asians. 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 [16].

For women with a positive screening test, the 100-g 3-hour 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-hour level of 180 mg per dL (10.00 mmol per L), 2-hour level of 155 mg per dL (8.60 mmol per L), or 3-hour 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 results are not available, intrapartum vancomycin is recommended [17].

A 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. 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, as a result USPSTF concluded that evidence is insufficient to make a recommendation [18].

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.

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. However, the most commonly utilized assessments include the nonstress test, amniotic fluid volume, and the biophysical profile as well as the contraction stress test.

Nonstress test 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, has gestational diabetes, or has gestational hypertension.

Contraction stress test is also done 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 postdates, 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 are fewer than 50%, and a negative CST has absent decelerations.

A biophysical profile combines the nonstress test 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 acid base balance and academia. A score of 0–2 is given to each parameter.

Score of 8 or more is reassuring and indicates low risk for still birth

Score of 6 warrants further work up and is considered equivocal.

Score of 0–4 correlates well with 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 and the 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 the 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 last 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. The active phase is the most predictable, lasting an average of 5 h in first-time mothers and 2 h in mothers who have birthed before.

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 baby 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 save your energy and pace yourself. 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 [19].

Intrapartum Analgesia

Maternal request is a sufficient medical indication for pain relief during labor. Laboring patients are educated about the different available methods of analgesia. 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 [20].

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 be avoided. It also helps to control blood pressure in women with preeclampsia by alleviating labor 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 [21]. 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

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Contents

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Every family physician providing care to women of childbearing age should have an understanding of the effect that various medical conditions can have on pregnancy. Pregnancy has significant effects on the progression of many medical conditions; medical conditions coexisting with pregnancy can adversely affect pregnancy outcomes if not treated adequately and judiciously. The role of the family physician begins at preconception, advising patients with significant medical conditions, like diabetes and chronic hypertension, to ensure adequate control before planning a pregnancy. This chapter will address many of these medical conditions (see Table 1).

Infectious Diseases

Urinary Tract Infections

Urinary tract infections are the most commonly seen infectious condition in pregnancy (see chapter "► Urinary Tract Infections").

Asymptomatic bacteriuria (ASB) refers to positive urine culture in an asymptomatic patient and occurs in 2–7 % of pregnancies [1]. Up to 40 % progress to pyelonephritis in pregnant women [2]. UTI and pyelonephritis are associated with increased risks of preterm birth, low birth weight, and perinatal mortality.

The Infectious Disease Society of America in its 2005 guidelines recommended screening for and treatment of ASB in pregnancy with short-term (3–7 day) therapy with antimicrobials such as nitrofurantoin, cephalexin, amoxicillin, or fosfomycin. A follow-up culture is recommended to ensure resolution [3].

Acute cystitis is a symptomatic infection of the urinary bladder and can also be complicated by pyelonephritis if left untreated. The treatment regimen and follow-up is similar to that recommended for ASB.

Acute pyelonephritis is characterized by flank pain, nausea, vomiting, fever >38 °C, and costovertebral tenderness with or without cystitis symptoms. E. coli accounts for 70 % of these cases, and Proteus, Klebsiella, and Group B streptococcus comprise most of the remainder. Traditionally, pyelonephritis is treated with IV antibiotics until 24 h after the woman is afebrile. Blood cultures are obtained if there is another underlying comorbidity such as diabetes.

Recurrent pyelonephritis occurs in 6–8 % of cases, therefore low-dose antimicrobial prophylaxis for the remainder of the pregnancy after an episode of pyelonephritis is recommended [4].

Viral Hepatitis

Acute viral hepatitis is the most common cause of jaundice in pregnancy [5] (see chapter "► Diseases of the Liver"). Differential diagnoses include acute fatty liver of pregnancy; hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome; and intrahepatic cholestasis of pregnancy.

Hepatitis B (HBV) during pregnancy may present unique management challenges for the mother as well as the fetus. Acute HBV during

Table 1 Selected medical conditions during pregnancy

Infections	Urinary tract infection, cystitis, and pyelonephritis Viral hepatitis A, B, C HIV, herpes, syphilis, tuberculosis, measles
Cardiovascular diseases	Chronic hypertension
Hematologic disorders	Anemia, iron deficiency
Clotting disorders	Thromboembolic disorders, deep venous thrombosis, pulmonary embolism
Endocrine disorders	Diabetes, thyroid disorders
Respiratory disorders	Asthma
Neurological disorders	Seizure disorders, migraine, Bell's palsy
Muscular skeletal	Carpal tunnel syndrome
Special circumstances	Obesity, bariatric surgery, advanced maternal age, illicit drug use

pregnancy in itself is not associated with increased mortality or teratogenicity [5]. In the absence of advanced liver disease, pregnancy is well tolerated by women with chronic hepatitis B in general. However, liver function tests are monitored in each trimester and until 6 months postpartum to detect the possibility of a hepatitis flare. HBV DNA (viral load) should be obtained in cases when there is transaminase elevation. The perinatal transmission rate is as high as 90 % in HbeAg-positive mothers [6]. However, transplacental transmission is rare. Maternal serum HBV DNA levels also correlate with the risk of vertical transmission, in spite of proper administration of prophylaxis; however, prophylaxis with HBIG and first dose of HBV immediately after delivery reduces transmission rates dramatically. The mode of delivery does not appear to influence transmission rates. In hepatitis B, treatment can be considered during pregnancy in carefully selected women using Telbivudine and Tenofovir (FDA Category B).

Hepatitis C

Women chronically affected with hepatitis C (HCV) can have an uneventful pregnancy without worsening of liver disease or adverse effects to the fetus. Although some studies have recorded low birth weights, low Apgar scores, and neonatal jaundice, additional data are needed to prove a definite correlation to HCV infection.

According to one meta-analysis, the vertical transmission of HCV occurs exclusively in women having detectable levels of HCV RNA in the blood. The risk of transmission is usually about 5 %, but it is almost doubled in patients coinfected with HCV and HIV [7]. Other risk factors are IV drug use and HCV infection of peripheral blood mononuclear cells. Routine prenatal screening for HCV is not recommended; however, women with significant risk factors for HCV infection should be offered anti-HCV antibody screening (ACOG level B recommendation).

Hepatitis A (HAV)

Hepatitis **A** is primarily transmitted by the fecal-oral route. HAV is usually an acute self-limiting disease. Diagnosis is confirmed by a positive serum anti-HAV IgM. Treatment is supportive. Hospitalization for IV hydration may be necessary in cases with severe nausea and vomiting.

Tuberculosis in Pregnancy

Pregnancy is not a risk factor for tuberculosis (TB) and is not known to influence its pathogenesis or progression. Congenital transmission of TB is rare and mostly occurs with maternal coinfection with HIV. However, active TB in the mother can cause congenital or more commonly neonatal infection. Screening for latent TB infection (LTBI) is limited to women at high risk of progression from LTBI to active TB, i.e., women with HIV, recent infection, or those who are otherwise immunocompromised. Treatment for LTBI is restricted to these high-risk groups, and the drug of choice is isoniazid along with pyridoxine supplementation. Active TB (except for monoresistant or multidrug-resistant strains) in pregnancy is treated with isoniazid, rifampicin, and ethambutol for 60 days followed by a 2-day-per-week regimen of rifampicin and isoniazid for 7 months [8]. In pregnancy, the use of pyrazinamide is limited to patients with extensive disease, TB meningitis, drug resistance, or HIV coinfection. Aminoglycosides are not recommended during pregnancy.

HIV in Pregnancy

All pregnant women should receive HIV screening in early pregnancy (see chapter "▶ Human Immunodeficiency Virus Infection and Acquired Immunodeficiency Syndrome"). All pregnant HIV-infected women should receive combination antiretroviral therapy (CART) regardless of HIV RNA viral load or CD4 T lymphocyte count. Antepartum, intrapartum, and infant antiretroviral (ARV) prophylaxis is recommended to reduce

perinatal transmission. The patient should receive counseling about the importance of adherence to ARV regimens. The National Perinatal HIV Hotline is available for free consultation on all aspects of perinatal HIV care (by phone:1-888-448-8765, by web http://www.ucsf.edu/hivcntr/Hotlines/Perinatal.html). All ARV exposure during pregnancy should be reported to the Antiretroviral Pregnancy Registry. A protease inhibitor (PI)–based regimen poses a slight increase in the risk of preterm birth. In antiretroviral naïve HIV-infected pregnant women, immediate start of therapy versus its delay until 12 weeks is often determined by CD4 lymphocyte count, HIV RNA levels, and maternal condition [9]. The coordination of services among primary care, HIV specialty care providers, mental health, and public health programs is needed to ensure CART adherence. In 2014 the Department of Health and Human Services published updated guidelines for evaluation and management of HIV-infected pregnant women [10].

Genital Herpes Simplex

Transmission of maternal herpes simplex virus (HSV) to neonate usually occurs during labor and delivery. Treatment with acyclovir is considered safe throughout pregnancy (see chapter "▶ Sexually Transmitted Diseases").

In women with prodromal symptoms or active lesions of HSV, cesarean delivery is recommended to reduce if not eliminate the possibility of neonatal HSV infection [11].

Measles

In late 2014, a significant outbreak of measles occurred in the United States. Pregnant women are among the patients who face particularly high risks for complications from this disease. Postexposure prophylaxis with IVIG is recommended in pregnant women without evidence of measles immunity [12]. MMR vaccine is contraindicated during pregnancy.

Syphilis

The CDC recommends screening of all pregnant women for syphilis at their first prenatal visit and a repeat test in the third trimester in those at high risk (see chapter "▶ Sexually Transmitted Diseases"). Untreated syphilis in pregnant woman can lead to its transplacental transmission resulting in perinatal death or congenital anomalies and congenital syphilis in the neonate with long-term sequelae. Penicillin is the gold standard for the treatment of syphilis and the only acceptable option in pregnancy. In pregnant patients who have a major penicillin allergy, treatment with penicillin after desensitization is recommended [13].

Cardiovascular Disease

Chronic Hypertension in Pregnancy

Chronic hypertension (CH) is defined by ACOG as blood pressure $\geq$140 mmHg systolic and/or $\geq$90 mmHg diastolic before pregnancy or before 20 weeks of gestation, the use of antihypertensive medications before pregnancy, or the persistence of hypertension for more than 12 weeks after delivery [14] (see chapter "▶ Hypertension").

It is important to distinguish chronic hypertension from new-onset hypertensive complications of pregnancy (see Table 2).

Chronic hypertension (CH) is estimated to occur in 3–5 % of all pregnancies [15]. Major risk factors include advanced maternal age and obesity.

In the African-American population, there is a higher prevalence of chronic hypertension, and it tends to occur at younger ages [15]. Despite increasing prevalence, the majority of women with chronic hypertension do well in pregnancy. However, some women develop complications such as superimposed preeclampsia, placental abruption, preterm birth, fetal growth restriction, and an increased likelihood of cesarean delivery [16].

Women with chronic hypertension planning pregnancy should receive preconception

Table 2 Various hypertensive disorders in pregnancy

Chronic hypertension	Gestational hypertension	Preeclampsia	Chronic hypertension with superimposed preeclampsia
Onset before 20 weeks of gestation and persists after 12 weeks post delivery	Onset after 20 weeks of gestation in a previously normotensive woman	Onset after 20 weeks of gestation with proteinuria	New onset of proteinuria in hypertensive woman after 20 weeks of gestation

counseling including evaluation for the presence of end organ damage and choosing an antihypertensive agency that is safe in pregnancy. The effect of lifestyle modifications such as weight management and healthy diet adaptations on pregnancy outcomes needs to be studied.

Management During Pregnancy

The ACOG recommends that blood pressure in women with uncomplicated hypertension be maintained between 120/80 and 160/105 mmHg. Further, it recommends initiating antihypertensive treatments when blood pressures are consistently more than 150 mmHg systolic and/or 100 mmHg diastolic. Tapering of antihypertensives is recommended when blood pressures consistently fall below 130/80 mmHg [16]. Alpha-methyldopa, labetalol, and nifedipine are among commonly used antihypertensive agents for CH in pregnancy. ACEs and ARBs are contraindicated in pregnancy.

There is a consensus in the guidelines that women with CH who are at high risk for preeclampsia should be treated with low-dose aspirin.

Pregnant women with CH are recommended to have more frequent prenatal visits to monitor blood pressures, urine protein, fundal height, maternal symptoms, and surveillance of fetal well-being, although there is no consensus regarding the most appropriate tests or intervals for ultrasound evaluation, NST, and biophysical profiles [14].

Clotting Disorders

Venous Thromboembolism (VTE) in Pregnancy

Venous thromboembolism (VTE) includes deep venous thrombosis (DVT) and pulmonary embolism (PE) (see chapter "▶ Venous Thromboembolism"). VTE complicates 0.1 % of pregnancies, and PE is the seventh leading cause of maternal mortality. Pregnancy in itself is a major risk factor for VTE. Others include thrombophilia, BMI $\geq$30, age $\geq$35 years, diabetes, infection, dehydration, multiparity, prolonged immobility during travel or bed rest, and smoking. Strikingly, in pregnancy DVT is 90 % more common in the left lower extremity than the right due to compression of left iliac vein by the right iliac artery [17].

Inherited thrombophilias include factor IV Leiden mutation, prothrombin G2021OA mutation, antithrombin III, and protein C or S deficiency. Pregnancy is a hypercoagulable state and leads to a decrease in protein S and resistance to activated protein C. A natural rise of D dimer in pregnancy limits its diagnostic value in detection of intravascular clotting.

The Wells score is not validated in pregnancy; however, the LEFt clinical prediction rule (left sided symptoms, edema, first trimester) might be an alternative [18]. The diagnosis of pulmonary embolism (PE) in pregnancy presents a clinical dilemma due to its overlap with normal symptoms in pregnancy like dyspnea.

The American Thoracic Society 2011 recommendations define a chest radiograph (CXR) as the first imaging procedure; lung scintigraphy is the preferred test in when the CXR is negative. CT pulmonary angiogram (CTPA) is used when a VQ scan is nondiagnostic, and clinical suspicion is

still high [19]. Radiation risk of theVQ scan and CTPA are balanced against the 20–30 % risk of maternal mortality from untreated PE. Gadolinium contrast is listed as category C in pregnancy by the US FDA.

Treatment of VTE in pregnancy based on American College of Chest Physician guidelines: subcutaneous low molecular weight heparin (SC LMWH) is preferred due to efficacy, ease of use, and safety profile [17]. Intravenous (IV) unfractionated heparin (UFH) is used in patients with persistent hypotension. SC LMWH treatment is withheld at least 24 h prior to planned delivery by C-section or induction. Patients with a high risk for recurrence of VTE are switched to IV UFH which can be stopped 4–6 h prior to delivery. Temporary IVC filter placement is reserved for patients having limited cardiopulmonary reserve. A heparin regimen can be resumed 6–12 h after delivery and continued for at least 6 weeks postpartum or longer depending on associated risk factors.

Hematologic Disorders

Anemia in Pregnancy

Hematologic changes in pregnancy include physiological anemia, neutrophilia, mild thrombocytopenia, and an increase in procoagulant factors (see chapter "▶ Anemia"). The CDC defines anemia in pregnancy as hemoglobin levels below 11 g/dL in the first and third trimesters and below 10.5 g/dL in the second trimester [20]. Patients with iron deficiency anemia (IDA) may present with fatigue, malaise, and pica. The fetus is usually spared any significant morbidity as a result of maternal IDA because iron is preferentially transmitted to the fetoplacental unit. IUGR is reported in patients with IDA when hemoglobin levels fall below 6.5 g/dL. Oral iron therapy often worsens the bloating and constipation in pregnant women resulting in poor adherence to therapy. Parenteral iron therapy is considered FDA Category C and therefore limited to selected groups.

Endocrine Disorders

Diabetes in Pregnancy

In recent years diabetes management in pregnancy has improved significantly (see chapter "▶ Diabetes Mellitus"). Although nine out of ten diabetics in pregnancy can be classified as gestational diabetes mellitus (GDM), pregestational type I or II diabetes tends to be associated with higher rates of maternal and fetal complications.

The ACOG recommends early pregnancy screening for diabetes with fasting or random blood sugar in women with risk factors such as history of GDM. All other patients should be screened between 24 and 28 weeks of pregnancy (1 h glucose test value of 140 mg/dl or less). Once a diagnosis of diabetes is confirmed, counseling and dietary consultation are imperative. Careful monitoring of plasma glucose to a goal of 105 mg/dl fasting and 140 mg/dl 1 h postprandial is recommended. Fetal ultrasonography is recommended to evaluate the presence of malformations, fetal growth, and biophysical profile. Patients not well controlled on insulin may need be referred to a perinatologist.

Pregestational diabetes was historically classified using the White classification. However, it is believed that presence or absence of vascular complications is a better predictor of pregnancy outcome [21].

Glycated hemoglobin reflects control over prior weeks and is helpful in counseling and assessing the risk of congenital abnormalities. Additional tests obtained to assess comorbidities are renal function tests, 24 h proteinuria quantification, thyroid function, EKG if hypertensive, and dilated eye exam to rule out retinopathy. The patient should be counseled regarding adherence to dietary recommendations as well as exercise and medications, as well as more frequent prenatal visits.

The ACOG recommends antepartum monitoring including fetal movement counting, NST, and biophysical profile as early as 32 weeks. The incidence of preeclampsia in patients with diabetes without vascular complications is 8 % and is

17 % among those with vascular disease [22]. Timing of delivery for women with well-controlled pregestational diabetes and without vascular disease is recommended at ≥39 weeks [23]. Those pregestational diabetics with vascular disease, delivery as early as 34 weeks may be considered among patients with poor glycemic control and patients with other obstetric indications such as preeclampsia, fetal growth restriction, and nonreassuring fetal surveillance. Maternal pregestational diabetes alone is not an indication for cesarean birth in absence of usual obstetric indications. The ACOG recommends prophylactic caesarean birth for those patients with an estimated fetal weight greater than 4500 g to avoid comorbidities associated with shoulder dystocia. Induction of labor is not recommended if there is suspected fetal macrosomia [22].

Thyroid Disease in Pregnancy

Thyroid disease is second only to diabetes among endocrinopathies affecting women in the reproductive age-group [24] (see chapter "▶ Thyroid Disease"). In iodine-sufficient regions the most common causes of hypothyroidism are autoimmune thyroiditis and iatrogenic hypothyroidism after treatment for hyperthyroidism [25]. In addition, hypothyroidism can lead to fetal neurocognitive deficits and preterm birth. Radioiodine uptake scans are contraindicated during pregnancy.

Therefore, current guidelines recommend targeted screenings of women at risk including those with history of thyroid disease or type-1 diabetes. Indications for thyroid testing in pregnancy include current thyroid hormone or other therapy, family history of autoimmune thyroid disease, and goiter. The incidence of overt hypothyroidism (elevated TSH and low free T4) during pregnancy is estimated to be 0.3–0.5 % and that of subclinical hypothyroidism (elevated TSH with normal T4 levels) to be 2–3 %. TSH levels should be checked every 4–6 weeks. The levothyroxine dose should be adjusted to keep TSH levels around 3 mIU/L. Ultrasonography is recommended for fetal growth and surveillance. Hyperthyroidism is less common than hypothyroidism with an approximate incidence during pregnancy of 0.2 %. Graves' disease accounts for 95 % of cases of hyperthyroidism; other less common causes include gestational trophoblastic disease, nodular goiter, and viral thyroiditis. Transient hyperthyroidism can be associated with hyperemesis gravidarum [25]. If left untreated during pregnancy, hyperthyroidism leads to increased risk of miscarriage, placental abruption, hypertension, fetal goiter, and growth restriction.

Appropriate management of thyroid disorders leads to improved pregnancy outcomes. In pregnant women with hypothyroidism levothyroxine is titrated to achieve a goal TSH of less than 2.5 mIU per liter (SORT recommendation level A), whereas patients with hyperthyroidism are treated with antithyroid medications (Methimazole after the first trimester of pregnancy) to keep free thyroxine levels in the upper third of the normal range.

Respiratory Disorders

Asthma in Pregnancy

Asthma is the most common respiratory disorder complicating pregnancy (see chapter "▶ Selected Disorders of the Respiratory System"). The effect of pregnancy on asthma is variable. The goal of effective management of asthma during pregnancy should be prevention of asthma exacerbations. Pharmacological therapy for asthma aims to control symptoms and achieve lung function at the lowest effective dose of medication [26]. Rescue agents (short-acting beta agonists) are used on as needed basis to treat acute symptoms. A recent study suggested that the use of inhaled corticosteroids was unlikely to contribute to adverse effects on fetal growth and development [27]. Studies have also suggested that pregnant women may benefit from asthma self-management education as a part of their obstetric care [28].

Lower Respiratory Infections

Pregnant women, especially smokers, are more prone to the development of bronchitis and pneumonia (see chapter "▶ Selected Disorders of the Respiratory System"). The diagnosis of pneumonia may be delayed, as clinicians often refrain from ordering chest radiographs. *Streptococcus and Mycoplasma pneumoniae* are common organisms causing pneumonia in pregnancy. Decreased tidal volume during later pregnancy due to an enlarging uterus may lead to complications of pneumonia such as empyema and respiratory failure. Chest radiography with appropriate shielding is recommended to confirm a diagnosis of pneumonia. Pneumonia in pregnancy is commonly treated in the inpatient setting, although ambulatory treatment may be reserved for selected cases with close monitoring. Choice of antibiotics is guided by culture results, and epidemiological resistance patterns of the organism involved.

Neurological Disorders

Seizure Disorders in Pregnancy

Seizure disorder is one of the most frequent major neurological conditions in pregnancy (see chapter "▶ Seizure Disorders"). During pregnancy approximately 60 % of patients have no change in frequency of seizures while 30 % report an increase in seizures.

Continuation of antiepileptic drugs (AEDs) is a necessity for most women with epilepsy. AEDs easily cross the placenta to the fetus. This poses a risk of teratogenicity; its extent is dependent on the drug, doses, timing of exposure, and genetic predisposition of mother and fetus. Also, there is increasing evidence to associate prenatal exposure AEDs to negative physical and neurodevelopmental outcomes in childhood [29].

Women with epilepsy should receive preconception counseling regarding the risks and benefits of AEDs (see Table 3). The antiseizure medication should be selected and optimized in consultation with a neurologist and if possible a maternal fetal medicine specialist. High-dose folic acid supplementation is recommended for all patients taking AEDs.

Table 3 AEDs and major fetal risks

AEDs	Major fetal risk
Topiramate, carbamazepine	Craniofacial anomaly
Phenolbarbital, phenytoin	Teratogenesis, coagulopathy
Valproic acid	Spina bifida

Migraine in Pregnancy

Migraines affect one in every five women in their reproductive years (see chapter "▶ Headache"). Therefore, it is imperative that women with migraines are counseled about safe and effective prophylaxis as well as symptomatic treatment. It is noted that two out of three patients with preexisting migraine report improvement of migraine during pregnancy; [30] those whose symptoms persist through the first trimester are likely to continue through the postpartum period [31]. Although there is no direct evidence linking migraine with adverse pregnancy outcomes [32], a number of studies have suggested an increased incidence of preeclampsia especially in obese migraineurs. Migraine is also considered to be a risk factor for pregnancy-related stroke [33].

Indications for imaging are similar to those for nonpregnant migraineurs. Although MRI is considered safe in pregnancy, iodine-containing contrast media should be avoided as it may cause fetal thyroid suppression.

Migraine trigger prevention is achieved by encouraging regular meals, adequate hydration, exercise as tolerated, and sleep hygiene. Acetaminophen is still the drug of choice for mild to moderate migraine, and NSAIDS should be avoided after 30 weeks of gestation. Antiemetics such as metoclopramide and promethazine can be given in pregnancy for symptomatic relief. Sumatriptan may be used in pregnancy if other treatments mentioned previously fail (FDA Category C). Propranolol, amitriptyline, and SSRIs such as escitalopram are used in

pregnancy for migraine prophylaxis (FDA Category C) in the lowest effective doses. Some studies have suggested that nonpharmacological, preventive methods like acupuncture and biofeedback may be beneficial during pregnancy [34].

Bell's Palsy

Bell's palsy (BP) is defined as acute peripheral facial paralysis resulting from inflammation and edema of the seventh cranial nerve as it exits from the stylomastoid foramen (see chapter "▶ Selected Disorders of the Musculoskeletal System"). Its prevalence increases two- to fourfold during pregnancy [35]. The suggested potential etiology is hypercoagulability leading to thrombosis of the vasa nervorum [36].

Other than its association with preeclampsia, no increase in adverse obstetrical outcomes among patients with BP have been noted [37]. The long-term outcome appears slightly worse in pregnant women, which is attributed to the fact that pregnant women are less likely to receive treatment for BP. However, the treatment recommended for pregnant women, except during first 9 weeks of gestation, is the same as for nonpregnant patients [38].

Musculoskeletal Disorders

Carpal Tunnel Syndrome

Carpal tunnel syndrome (CTS) typically presents as paresthesias and pain of the first three fingers, often bilaterally resulting from compression of median nerve in the carpal tunnel (see chapter "▶ Selected Disorders of the Musculoskeletal System"). Pregnancy accounts for 7 % of cases of CTS among women of childbearing age [39]. Symptoms usually occur during the third trimester. Half of patients report persistence of CTS 1 year after delivery, and symptoms may recur in subsequent pregnancies [40]. Patients may receive symptom relief from a wrist splint used in neutral position throughout the day and night. Surgical intervention (release of flexor retinaculum) or local corticosteroid injection are rarely indicated in the absence of motor weakness or atrophy. In a 3 year prospective study of pregnant women with age-matched controls, the pregnancy cohort showed significantly better outcomes than nonpregnant controls [41].

Special Circumstances in Pregnancy

Obesity and Pregnancy

Even modest increases in preconception BMI are associated with increased risk of perinatal morbidity and mortality (see chapter "▶ Care of the Obese Patient"). In addition, these pregnant women may experience greater risks of obstructive sleep apnea, hypertension, diabetes, VTE, and anesthesia complications. Weight management guidelines for women who plan pregnancies should take these findings into consideration to reduce these complications [14].

Pregnancy After Bariatric Surgery

Currently, it is recommended that women delay pregnancy for 12–18 months after bariatric surgery. The starvation phase may be dangerous for both mother and fetus. Although malnutrition may not increase the risk of congenital defects, it can increase risk of "small for gestational age" and preterm-birth infants [42].

Advanced Maternal Age in Pregnancy

In the past half century, changing socioeconomic patterns have led to an increase in the incidence of advanced maternal age. In 2011 alone, 1 in 12 women gave birth to their first child at age greater than or equal to 35 years, and 1 in 7 of all childbirths in the United States were to women in that age-group [43].

The prevalence of medical and surgical morbidities such as obesity, cardiovascular diseases, and cancers increase with advancing maternal age. Diabetes and hypertension, gestational and

pregestational, both occur at higher rates in older women especially among those who are overweight. Women greater than or equal to 35 years of age also should be counseled to expect at least twofold increased rate of cesarean delivery, hospitalization, and medical complications than their younger counterparts. Vigilant monitoring and fetal surveillance when indicated may improve pregnancy outcomes in these patients.

Illicit Drug Use in Pregnancy

In the United States 15.4 % of pregnant women admit to smoking cigarettes, 5.4 % admit to the use of illicit drugs, and 9.4 % reported drinking alcohol in the previous month [44]. The ACOG therefore recommends screening for substance abuse during first prenatal visit. The CRAFFT screening tool is available for use without restriction [45]. In addition to smoking tobacco, opiates, marijuana, cocaine, amphetamines, alcohol, and prescription psychotherapeutics are substances that are commonly abused by pregnant women. Positive tests for illicit drugs also have legal ramifications. There are state requirements for notification; therefore an informed consent is needed from the patient unless she is unable to consent (e.g., due to intoxication). Clinical manifestations can arise from the use, overdose, or withdrawal of these substances. Multiple obstetric complications such as fetal growth restriction, placental abruption, preeclampsia, prematurity, premature rupture of membranes, miscarriage, and fetal death can result from substance abuse during pregnancy especially opiates, alcohol, and cocaine [46]. A multidisciplinary team approach by the family physician, social service provider, addiction medicine, and fetal maternal medicine specialists may be needed for the management of these patients.

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Obstetric Complications During Pregnancy

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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 than 20 mm without an identifiable embryo or presence of an embryo with a crown-rump length greater than 5 mm without a heartbeat are 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 not smoking, drinking alcohol, or 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 spontaneously without intervention. In women with significant bleeding, pain, or infection, either medical or surgical intervention should be considered [5]. 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 in the 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 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 an

ectopic 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 non-viable 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 heart beat 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, no evidence of rupture, and if a mass is detected it is <3 cm in diameter and no fetal heart beat 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 one 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 heart beat, 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 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, 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].

Prevention

A Cochrane review of prophylactically treating women with increased risk of developing preeclampsia with low dose aspirin demonstrated that the number 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 wellbeing 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 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 two 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 is 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 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, over distension 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 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 hominus 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 wellbeing 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

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	

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 34 weeks has been associated with preterm delivery. 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, 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.

Although several studies have examined the treatment of asymptomatic bacterial vaginosis in the prevention of preterm labor and delivery, data remains conflicted. The U.S. 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 [44].

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 4 doses 6 h apart have been shown to be effective in decreasing perinatal morbidity and mortality [45]. 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 rate of cerebral palsy in their infants [46].

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 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 [45]. 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 [47].

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 unites every 4 h through delivery should be administered [48]. 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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Family Medicine
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Problems During Labor and Delivery

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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

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 a trial of labor after cesarean (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 morbidity and mortality both for the mother and fetus. Uterine rupture usually involves the previous hysterotomy scar but may extend in the uterine wall or beyond. Risk factors include excessive oxytocin administration, dysfunctional labor, history of more than one cesarean, multiparity, and history of nonpregnant uterine perforation. Rates of rupture have been estimated at 4–9 % after a classical incision, 0.5–1.5 % after a low transverse incision, and 1–4 % after a low vertical incision [2]. Its presentation most frequently involves 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. Urgent laparotomy may be indicated for any of these findings, as fetal death or adverse neonatal neurologic outcomes may occur in as many as 20–25 % of cases of uterine rupture.

Approach to the Patient

While decreasing the occurrence of repeat cesareans would be an obvious benefit, comparing 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. A calculator is available on the

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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

website for the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network (https://mfmu.bsc.gwu.edu), which allows for more individualized counseling of pregnant patients with a prior cesarean. The decision 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, 3].

Management

The most recent ACOG practice bulletin on this issue made a number of recommendations based on "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 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. 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, 4].

Indications for Cesarean Delivery

Cesarean delivery was once considered the last resort, resulting in maternal death in the majority of cases [5]. 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 %) [5, 6]. See Table 1 for a helpful categorization of cesarean indications, suggested in *Munro Kerr's Operative Obstetrics* [5]. Frequently, a combination of relative indications, rather than one absolute indication, leads to the decision for cesarean.

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Breech Delivery

Background

The Term Breech Trial in 2000 led to a dramatic change in obstetric practice [7]. When compared with planned cesarean delivery, the study demonstrated increased morbidity with planned vaginal breech delivery. Follow-up analyses have not been consistent in suggesting increased long-term risk [8, 9], but hesitance to plan vaginal breech deliveries has persisted. ACOG expresses support for a general policy of cesarean delivery for these patients [10].

General Principles

Breech presentation persists in approximately 3–4 % of singleton pregnancies at term [6]. 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 [6]: 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 aftercoming head.

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 [6].

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.

Placenta Abruption

Placenta abruption occurs when there is premature separation, either partial or total, of the placenta prior to birth. Placenta abruption occurs in 0.4–1 % of pregnancies [11]. Half of women who experience placenta abruption have hypertension. Other risk factors for placenta abruption include abdominal trauma, grand multiparity ($\geq$3), uterine anomalies, folate deficiency, short umbilical cord, cigarette smoking, cocaine usage, history of abruption, and maternal age over 35 [11, 12]. Most women will experience third trimester bleeding (80 %), pain (50 %), or a non-reassuring fetal heart rate tracing.

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Ultrasonography does not always detect a clot underneath the placenta. Therefore, placenta 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 is seen in 0.4–0.6 % of all births [12]. 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 on second trimester ultrasounds. If the placenta previa is marginal, they tend to resolve in 95 % of cases. Placenta previa is usually diagnosed in asymptomatic women during ultrasonography examination (transvaginal ultrasound is superior). 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 [12]. 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 recommended to administer steroids in case preterm delivery is necessary. Cesarean section for complete and partial placenta previas is usually performed at 36–37 weeks of gestation [12].

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 [12]. The incidence of accreta is rising due to the rise in cesarean delivery rates [12] and is estimated to occur in between one in 533–2510 deliveries. Other uterine surgeries, advanced maternal age, and multiparity can also increase risk of placenta accreta. 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 followed by total abdominal hysterectomy without an attempt to separate the placenta from the uterus to avoid excessive bleeding. 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 [12].

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 % [12]. Vasa previa occurs in 1 in 2500 deliveries [12]. Risk factors include a low-lying placenta, placenta with accessory lobes, multiple

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pregnancies, and pregnancies from in vitro fertilization [12]. 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 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 3 % of all pregnancies [13].

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, infection, second or third trimester bleeding, cerclage, shortened cervical length, uterine overdistention, smoking, 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.

There is an increased risk of chorioamnionitis and endometritis if time from rupture to delivery is >12 h. Neonatal infection is associated with chorioamnionitis and positive maternal GBS status in women with term PROM. Other complications include placental abruption, umbilical cord compression during labor, and umbilical cord prolapse.

Diagnosis

Women will present with a gush of fluid in both PROM and PPROM. It is interesting to note that patient history of a gush of fluid is 90 % sensitive for PPROM [14]. On exam, the clinician should look for pooling of fluid and do a visual assessment of cervical effacement and dilation. The clinician can also perform a nitrazine test, ferning examination, or an AmniSure/AmnioSense to confirm rupture of membranes.

Treatment

Women presenting with PROM should be induced, usually with IV oxytocin, although misoprostol can also be considered. In the setting of PROM, antibiotics may reduce chorioamnionitis and endometritis; however, it has not been shown to improve neonatal outcomes. Thus, the routine use of antibiotics without confirmed maternal infection should be avoided in PROM [15]. 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 $\geq$34 weeks of gestation: Delivery is recommended with induction of labor. GBS prophylaxis is based on prior culture results or risk factors.
- PPROM at 24–33 weeks of gestation: Expectant management until 33 weeks if lung maturity is not proven. Treatment with antibiotics, corticosteroids, and intrapartum GBS prophylaxis is recommended. Consider the use of magnesium sulfate for fetal neuroprotection if there is a risk of delivery before 32 weeks of gestation.

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- PPROM at <24 weeks of gestation (previable): Counsel regarding risks and benefits; including likely neonatal morbidity and mortality, compare immediate delivery vs. expectant management. No GBS prophylaxis necessary. Monitor for signs of infection. Corticosteroids are not recommended until fetus has reached viability.

Postterm Pregnancy

General Principles

Postterm pregnancy refers to a pregnancy that is ≥42 $^{0/7}$ 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 [16]. 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 % [17].

One risk factor for postterm pregnancy is inaccurate dating. Of the true postterm pregnancies, most have no known etiology. Women at highest risk for postterm pregnancy are those with a previous postterm pregnancy. The risk of a second postterm birth is increased two- to threefold and quadruples after two prior postterm pregnancies [18]. Other risk factors for postterm pregnancy include nulliparity, male fetus, maternal obesity, older maternal age, and Caucasian ethnicity.

Postterm fetuses tend to be larger than term fetuses, further increasing their risk of prolonged labor, shoulder dystocia, meconium-stained amniotic fluid, and cephalopelvic disproportion. These complications increase the risk of birth injury. Beyond 42 weeks of gestation, the perinatal mortality rate is twice the rate at term (4–7 deaths vs. 2–3 deaths per 1000 deliveries) [19]. Other risks to the fetus include low umbilical artery pH, low 5-min Apgars, and an increased probability of death in the first year of life.

Maternal complications of a postterm pregnancy include increase in labor dystocia, fetal macrosomia, failed induction, third or fourth degree lacerations, postpartum hemorrhage, and increased risk of cesarean section. A postterm pregnancy can also be a cause of emotional distress to the mother.

Management

In well-dated postterm pregnancies, it is recommended to induce after 41 $^{0/7}$ weeks of gestation regardless of cervical status in order to reduce perinatal mortality and meconium aspiration syndrome [20]. 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 [6]. 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 likely the most common indication for primary cesarean

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delivery [21, 22], as well as the underlying factor in at least one third of all cesarean deliveries [2, 23], and therefore a significant public health concern. The problem is significantly more common in nulliparas than multiparas. Consequently, 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, 6], 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 [6] 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 [6], 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 [24].

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 [6]. 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. Especially in the case of nulliparous patients, this will often be accomplished with the use of oxytocin, which is very safe in this group of patients. These steps will also include accurately quantifying the contractions.

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 and as oxytocin is comparatively safe. 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" [25]. The protocol achieved remarkable success – one highlight being a 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.

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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-fatality rates as high as 50 % [26]. Guidelines issued in 1996 and 1997 recommended intrapartum antibiotic prophylaxis to prevent neonatal GBS disease [26]. This was followed by guidelines in 2002 recommending universal culture-based screening for GBS colonization in pregnant patients at 35–37 weeks of gestation [26]. These efforts have led to an 80 % reduction in the incidence of early-onset neonatal sepsis due to GBS. Despite this significant progress, GBS remains the leading cause of neonatal infectious morbidity and mortality [27].

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 [26]. The recommendations for intrapartum management discussed below come from the Centers for Disease Control and Prevention (CDC) 2010 revised guidelines [26], which were officially endorsed by ACOG in 2011 [27].

Intrapartum GBS prophylaxis is 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, or an intrapartum fever. 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.

Chorioamnionitis

General Principles

Chorioamnionitis, also termed "intra-amniotic infection" (IAI), is acute inflammation of the placenta and chorion [28]. Most commonly, IAI is caused by polymicrobial bacterial infection ascending from the lower genital tract. IAI may account for half of deliveries prior to 30 weeks and up to 40 % of cases of early neonatal sepsis and pneumonia [29].

Risk factors for chorioamnionitis 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 [29]. Potential maternal complications of chorioamnionitis include maternal bacteremia, postpartum endomyometritis, and postpartum hemorrhage. Potential fetal complications include death, asphyxia, sepsis, cerebral palsy, and long-term neurodevelopmental disability [28]. The majority of fetal and neonatal complications are significantly more common with decreasing gestational age.

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Diagnosis

The common diagnostic criteria for chorioamnionitis are maternal fever with two or more of the following: maternal leukocytosis, maternal tachycardia, fetal tachycardia, uterine tenderness, or foul-smelling amniotic fluid [2]. 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 chorioamnionitis is straightforward. As soon as the diagnosis of chorioamnionitis is made, antibiotics should be initiated, as immediate treatment with antibiotics has been shown to reduce maternal and neonatal complications [28]. The typical antibiotic regimen includes ampicillin and gentamicin, with the addition of clindamycin if a cesarean section is performed. One dose of antibiotics should be administered following delivery [28]. 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 [28]. Labor should be expedited in the setting of chorioamnionitis, 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 12 % of live births 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 [30].

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, chorioamnionitis, and endometritis are all more likely to occur with MSAF [31]. 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 [31]. MAS is the most serious complication associated with MSAF and can lead to intubation and mechanical ventilation, pneumothorax, seizures, and death [32].

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 [33]. 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 chorioamnionitis [33]. Because the rates of neonatal sepsis were similar regardless of antibiotics, there

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is insufficient evidence at this time to recommend administration of prophylactic antibiotics to laboring mothers with MSAF [33].

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 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 [32]. 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.

Shoulder Dystocia

General Principles

Shoulder dystocia is a relatively rare and uncomplicated condition but can become an obstetrical emergency. It occurs at delivery and is characterized by difficulty delivering fetal shoulders, requiring additional maneuvers to facilitate extraction. It is also defined as a head-to-body delivery time of greater than 60 s [34]. Shoulder dystocia affects 0.6–1.4 % of vaginal deliveries of fetuses in the vertex presentation [35]. Shoulder dystocia cannot be predicted or prevented. The goal is to understand the risk factors and signs of shoulder dystocia and then quickly respond when it does present.

Maternal risk factors include diabetes, postterm pregnancy, previous shoulder dystocia (recurs in up to 25 % of subsequent pregnancies), pelvic anatomy, short maternal stature (less than 5 ft tall), maternal obesity (over 200 lb), previous infant over 4000 g, or advanced maternal age. Fetal risk factors include macrosomia (estimated fetal weight over 4000 g), size inconsistent with dating, and male gender. Labor risk factors include operative vaginal delivery and abnormal progression of labor (either prolonged active or second-stage or precipitous delivery).

If the fetal shoulders remain in an anterior-posterior position during descent or descend simultaneously, then the anterior shoulder can become impacted behind the symphysis pubis, or the posterior shoulder may be 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.

Five percent of shoulder dystocias are complicated by neonatal injury, the most common complications being brachial plexus injury and clavicular fracture. Brachial plexus injury (Erb's palsy) occurs in 2–16 % of shoulder dystocias. Most cases resolve but it can result in permanent neurologic impairment. Clavicular fracture and humerus fractures usually have a benign course and complete recovery. Other more serious complications include pneumothorax, permanent neurological damage due to hypoxia, and death. Maternal complications include postpartum hemorrhage, third or fourth degree perineal lacerations, uterine rupture, bladder rupture, 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.

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Table 2 Maneuvers for managing shoulder dystocia

	Initial maneuvers
McRobert's	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

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 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 nor has an established sequence been determined. Knowledge of all the maneuvers is important so that the most appropriate maneuver is applied in each clinical situation.

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.

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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. 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 decreased [6]. 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 [5].

Approach to the Patient

The indications for forceps and vacuum delivery include conditions that threaten the well-being of the mother or fetus, as well as nonprogressive second-stage labor [5, 6]. Prerequisites for both forceps and vacuum application are largely the same [6]: complete dilation of the cervix, ruptured membranes, engagement of the fetal head, vertex presentation, no suspected cephalopelvic disproportion, 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.

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 [36]. 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. Potential benefits of forceps are increased likelihood of achieving vaginal delivery [37] 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 [37]. The likely decreased maternal risk is a potential benefit of the vacuum, though cephalohematoma may be more common [37]. 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, and traction should occur for the shortest amount of time possible.

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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 [38].

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 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 [39]. 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 [39].

There are spontaneous and iatrogenic risk factors for UCP. Spontaneous UCP can occur in uncomplicated pregnancies and are 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 multiparty, cord abnormalities (higher risk of prolapse with a thin cord), birth weight less than 2500 g (although some authors quote <1500 g) [40], and spontaneous rupture of membranes (57 % of cases occurred within 5 min of rupture) [41]. Iatrogenic causes include artificial rupture of membranes without an engaged presenting part, attempted rotation of the fetal head, amnioinfusion, and external cephalic version in patient with ruptured membranes, placement of an intrauterine pressure catheter or fetal scalp electrode, and placement of a cervical ripening 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

As the act of rupturing membranes, whether spontaneous or artificial, is a risk factor for cord prolapse, it is recommended that care be taken when considering 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 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.

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- 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.

Neonatal outcomes in cases of UCP are generally good when delivery can be accomplished within 30 min.

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Family Medicine
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Postpartum Care

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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 effective prenatal, intrapartum, and postpartum 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. However, in industrialized nations, it has become common practice for infants to be immediately whisked away for "transition" which includes a check of vital signs, maintaining temperature by placing on the warmer, medications, immunizations, and sometimes a bath. A Cochrane review of 34 randomized trials involving 2177 mothers and newborns concluded that babies who were immediately exposed to skin-to-skin contact (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].

The concept of maternal-infant bonding was introduced as far back as the 1960s [2, 3] through the work of Rubin and subsequently popularized by Klaus and Kennell in the 1970s [4]. 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 while the lack of this bond can have long-term negative effects on the maternal-child relationship. Some of these negative consequences include irritability, hostility, and lack of maternal feelings for the child which can progress to child abuse and neglect [3, 5]. Hospitals began to institute "rooming in" policies after the publication of the book *Maternal-Infant Bonding* by Klaus and Kennell in 1983 [6]. 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 touch, gaze, and talk to their babies [5, 7]. However, it is important to note that unlike animals, humans are able to form bonds with their infants and vice versa if

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separation is temporary and the infant's basic needs are being met [8]. Caution should be exercised in equating the interruption of maternal-infant bonding with future catastrophe.

Promotion of Breastfeeding

Part of the benefit of early maternal-infant bonding is the initiation and continuation of breastfeeding. Obstetric and pediatric physicians have a significant role to play in helping to ensure 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 [9]. 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 [10]. 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 [11]. 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 [12]. Hospitals that are certified as being "baby friendly" have the highest breastfeeding rates [10, 13].

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 1,000 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 [15]. 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 (posterior pituitary necrosis) [15].

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 1–2 min (assuming the newborn does not require resuscitation) has been shown to improve the hematologic status of newborns. Controlled

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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 [16].

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 [15].

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), 800–1,000 microgram PO, SL, or PR; methylergonovine (methergine), 0.2 mg IM every 2–4 h; or carboprost (Hemabate), 0.25 mg IM or imtramyometrially every 15 min up to 8 doses [15].

The clinician can evaluate for trauma as a cause of PPH by inspecting the vulva, vagina, and cervix for lacerations and hematomas. Uterine inversion is diagnosed by visual inspection of the cervix [15].

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 [15].

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 [15].

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 [16]. 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 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 4 weeks after delivery [17].

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Postpartum Infection

Postpartum patients are at risk for a number of postpartum infections, including endometritis, wound infection, urinary tract infections, mastitis, and pneumonia [18, 19]. 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 and physical exam. The value of a culture from the endometrium is limited and not usually indicated [19]. 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 [20], although preoperative antibiotic prophylaxis reduces the rate of endometritis [21]. 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 [22]. Intravenous antibiotics are continued until the patient has been afebrile for 24–48 h, the WBC count has normalized, and the patient is otherwise clinically stable [20]. There has not been shown to be any benefit of continuing oral antibiotic therapy after intravenous antibiotic therapy has been discontinued [22].

Postpartum wound infection is diagnosed by redness, swelling, drainage, and/or pain at the site of the Cesarean section or the episiotomy/perineal tear. Risk factors for post-Cesarean wound infection include prolonged labor/prolonged rupture of membranes, chorioamnionitis, obesity, and prolonged surgery [21]. 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) [21] and include *Staphylococcus aureus*, *Streptococci*, and gram-negative bacilli.

Urinary tract infections are diagnosed as in general medical patients by the presence of pyuria, usually accompanied by positive nitrate testing on the dipstick analysis. Urinary tract infections in the postpartum period are treated as in general medical patients. Similarly, pneumonia is diagnosed as in general medical patients 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 milk removal is an important component of treatment [23]. 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/clavulate unless methicillin-resistant *Staphylococcus aureus* is suspected, in which case clindamycin may be used. Breast abscess may arise as a complication of postpartum mastitis. Treatment involves drainage of the abscess and usually antibiotics. In most cases, breastfeeding may continue.

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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 cases were infants, 15 of whom died [24]. Vaccination during pregnancy will prevent hospitalization and death from pertussis. However, if the immunization is not received during pregnancy, it should be provided postpartum [24].

Rhogam

The Rh immune globulin (Rhogam) is given to an Rh-negative mother who gives 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. Typical dose is one vial of 300 mcg of Rhogam within 72 h if there is no evidence of fetal red cells in maternal blood. Otherwise, the quantity of fetomaternal hemorrhage determines how many vials of Rhogam are given [25]. The risk of rhesus alloimmunization can decrease from 1–2 % to 0.1 % if Rhogam is given at 28 weeks gestation and postpartum [26]. It is still acceptable to give Rhogam up to 28 days postpartum if it is not given within 72 h of delivery [27].

Postpartum Office Visit

The postpartum period begins an hour after delivery of the placenta though the subsequent 6 weeks. The postpartum office visit usually takes place at 6 weeks during which the physician addresses issues like breastfeeding, postpartum depression, complications including urinary incontinence, constipation, sexuality, and also contraception [28]. However, for some women, waiting till 6 weeks might be too late [29]. 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 as reasons [30]. Earlier visits and encouragement from the clinician may play a significant role in breastfeeding continuation. Fifty-five percent of women cited individualized encouragement by their clinician as reason for continuing breastfeeding up till 12 weeks postpartum [31]. Women in the adolescent age-group, recent immigrant status, lack of social support, history or predisposition to depression/bipolar/psychosis, and physician judgment are some indications to consider an earlier visit [29].

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 [29]. 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, and 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 [32]. Sexuality after childbirth can be affected by vaginal dryness, pelvic floor dysfunction, and decreased libido [33]. There is need for education for new parents both before and after childbirth as cultural beliefs and myths continue to play significant roles in sexuality in pregnancy and after childbirth.

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Postpartum Contraception

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 only 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 major maternal complications such as bleeding, anemia, infection, and even death [34]. A 3 year interval between births has been shown to decrease neonatal and post-neonatal mortality for the subsequent child [35].

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 [36]. Once supplemental feeding is introduced or menstrual bleeding starts, an alternative form of contraception becomes necessary [37]. 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. The WHO found a statistically significant reduction in milk volume among COC users when compared to users of progestin-only contraceptive pills [38, 39].

Postpartum Contraceptive Options

The WHO medical eligibility criteria (MEC) for contraception in postpartum women is more conservative than the US MEC (Table 1). The WHO MEC allocates category four level of risk for combined oral contraceptive use to breastfeeding women who are less than 6 weeks postpartum and category three for the same women using progestin-only contraception. Between 6 weeks and 6 months, the categories for combined OCP and progestin-only OCP are 3 and 1 respectively [40]. The WHO MEC is aimed at policymakers in developing countries where the risk of pregnancy far outweighs that of contraceptive use. See Table 2 below.

Postpartum Depression

The incidence of postpartum depression is approximately 13 % of all new mothers [41]. Routine screening for postpartum depression is recommended. The Edinburgh Postnatal Depression Scale [42] has been the most widely used validated screening tool. Risk factors for postpartum depression include previous postpartum depression, 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 [41]. 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].

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Table 1 Drafted from the 2010 US CDC medical eligibility criteria (MEC) for contraceptive use – summary report (For complete guidance, please see www.cdc.gov/reproductivehealth/unintendedpregnancy/USMEC.htm)

Condition	Sub-condition	Combined OCP	Progestin only OCP	Injection	Implant	Mirena IUD	Copper T IUD
Parity	Nulliparous	1	1	1	1	2	2
	Multiparous	1	1	1	1	1	1
Postpartum	<10 min post placenta	NA	NA	NA	NA	2	1
	>10 min–4 weeks		1	1	1	2	2
	<21 days	4	1	1	1	2	2
	>4 weeks		1	1	1	1	1
	21–42 days[a]	3	1	1	1		
	21–42 days[b]	2	1	1	1		
	>42 days	1	1	1	1	1	1
	Puerperal sepsis		1	1	1	4	4
Breastfeeding	<1 month	3	2	2	2	2	2
	One month or more	2	1	1	1	1	1
Postabortion	First trimester	1	1	1	1	1	1
	Second trimester	1	1	1	1	2	2
	Immediately post septic abortion	1	1	1	1	4	4

Key
1 No restriction (method can be used)
2 Advantages generally outweigh theoretical or proven risks
3 Theoretical or proven risks usually outweigh the advantages
4 Unacceptable health risk (method not to be used)
[a]Higher risk for recurrent DVT/PE
[b]Lower risk for recurrent DVT/PE
NA not applicable

Table 2 WHO guidelines for use of oral contraceptive pills (OCP) by breastfeeding status

Condition	Combined OCP	Progestin only OCP
Breastfeeding		
(a) <6 weeks	4	3
(b) 6 weeks–6 months	3	1
(c) >6 months	2	1
Non breastfeeding		
(a) <21 days[a]	3/4	1
(b) <21 days[b]	3	1
(c) 21–42 days[a]	2/3	1
(d) 21–42 days[b]	2	1
(e) >42 days	1	1

Key
1 No restriction (method can be used)
2 Advantages generally outweigh theoretical or proven risks
3 Theoretical or proven risks usually outweigh the advantages
4 Unacceptable health risk (method not to be used)
[a]Higher risk for recurrent DVT/PE
[b]Lower risk for recurrent DVT/PE

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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 postpartum women who develop thyroiditis is to initially develop transient thyrotoxicosis between 2 and 6 months postpartum. This is usually asymptomatic. This is often followed by hypothyroidism, but they usually return 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 as long as the patient is not trying to get pregnant.

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 all represent 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. A computed tomographic pulmonary angiogram is recommended for diagnosis in most patients. Postpartum pulmonary embolism has a relatively high mortality rate [48].

Management of Selected Common Postpartum Symptoms

Anemia is a common postpartum problem, and presentations vary by severity. Mothers can present with fatigue, pallor, dizziness, hypotension, and tachycardia. Treatment depends on the clinical scenario and can include blood transfusion or oral or parenteral iron supplementation.

A prior history of hemorrhoids and/or constipation are predisposing factors worsening hemorrhoidal symptoms postpartum. Common solutions are hydration and increased fiber intake, to avoid constipation. Perineal pain is a common complaint after vaginal birth especially in women who had prolonged second stage. Warm sitz baths, ice packs to the perineum, topical lidocaine, and analgesics are all treatment options.

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Genetic Disorders

Mylynda Beryl Massart

Contents

Introduction

This chapter will serve as an initial introduction to genomic medicine for the family medicine physician. Historically, family medicine physicians have recognized and managed many common genetic syndromes such as Trisomy 21, Klinefelter's 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, 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

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Table 1 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 sub specialist: Initiate a co-management plan, including treatment and diagnostic testing when indicated
6. Council 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

multiple genes, environmental, and lifestyle choices there will not be an adequate supply of Medical Geneticists and genetic counselors to meet the ever 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 Table 1). This chapter will provide the basic tools and references for additional resources to begin integrating these genetic competencies into practice.

Basic Science of Genetics

Terminology

Within normal cellular function, genes are the basic physical unit of inheritance which contain 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 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 variation 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.

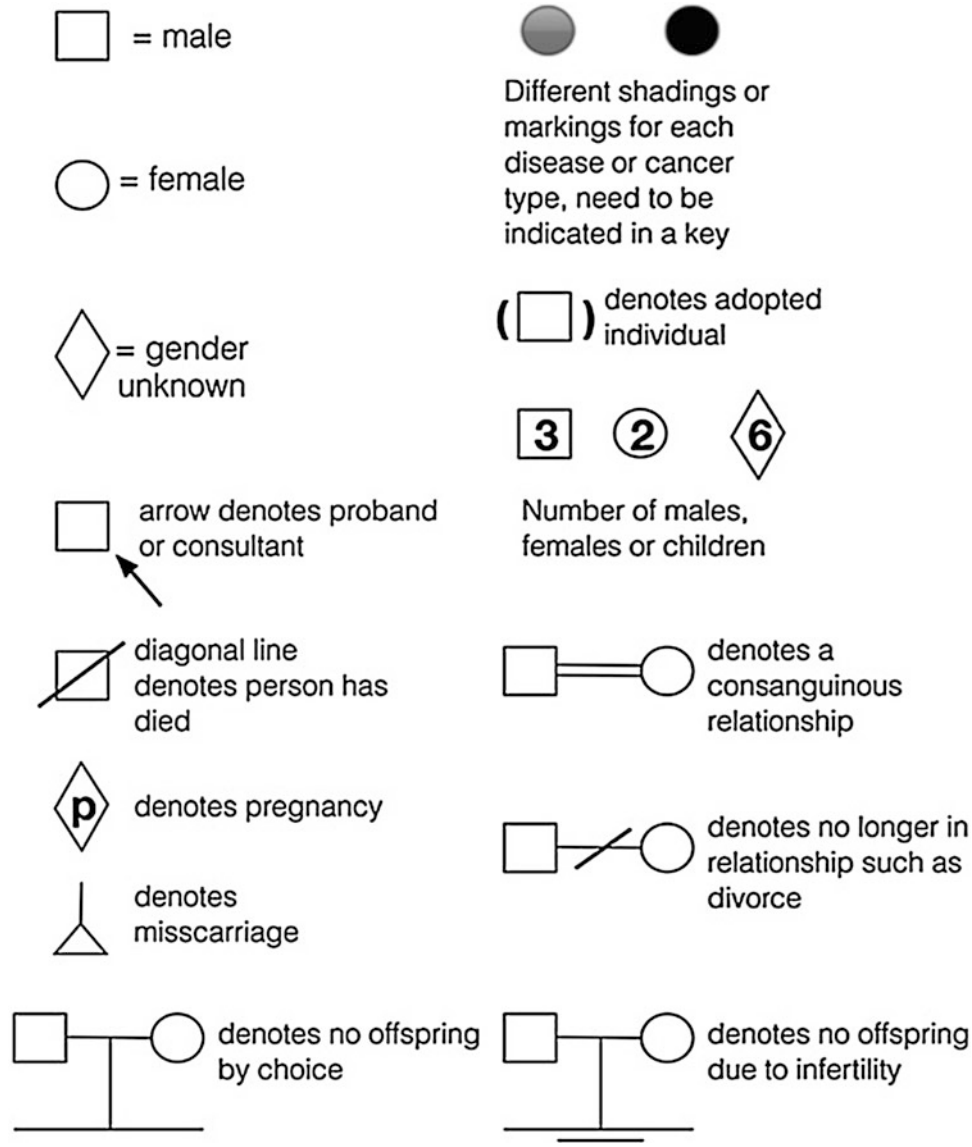
Once genetic variation occurs in the germ line, it can be passed on through several different modes of inheritance. Genetic diseases can be autosomal dominant, meaning that individuals who inherit one mutated copy of a gene will manifest the disease. In this type of inheritance, each affected individual 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 then females since males only need to inherit one copy of the mutated gene from their mother. While most syndromes are single gene disorders, the expression of these conditions are often strongly influenced by multiple factors. These may include combinations of mutations in multiple genes, as well as the impact from 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].

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 Table 2, and Fig. 1). The identification of two or more individuals on the same side of the pedigree with the same disease, or earlier onset of disease then 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

Table 2 Standard pedigree symbols

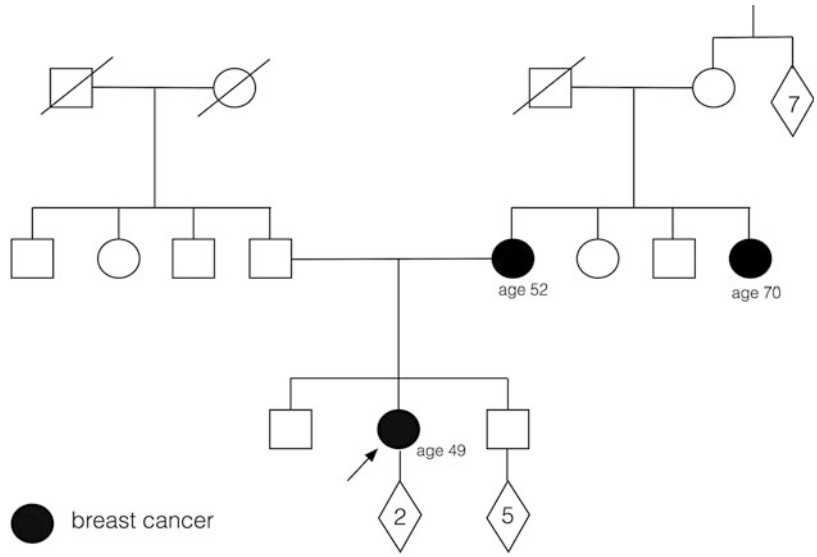


identifying the need for possible prenatal screening. The largest ethnic specific prenatal panel is the Ashkenazi Jewish genetic panel which tests for carrier status for Bloom syndrome, Canavan disease, cystic fibrosis, familial dysautonomia, Fanconi anemia group C, Gaucher disease, glycogen storage 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

Fig. 1 Sample pedigree



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 physician to coordinate any additional interventions, specialty care and therapies through their primary care medical home (see Table 3).

Some syndromes may not present until adulthood, for example, Klinefelter's 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 regards 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 amongst 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

Table 3 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
Familal hypercholesterolemia	Autosomal dominant
Fragile X	X-linked dominant
Galactosemia	Autosomal recessive
Gaucher	Autosomal Recessive
Hemachromatosis	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

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 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 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 27 companies offering DTC genetic testing on the market [13–15]. 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 $230 million by 2018 [13–15]. 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 [16]. 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 [16]. 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.

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 as well as 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 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

The genetics of drug metabolism has exploded over the last several years. Not all drugs affect each patient the same way and it can be very hard to predict who will respond well, who will not respond at all, and who will have an adverse reaction to a given medication [17]. Clinicians are now able to apply information regarding genetic variation to predict the effectiveness and potential for reactions to some medications on the individual patient level. The most common variation is the single nucleotide polymorphisms (SNPs). There are an estimated 11 million SNPs amongst the human population [18]. Interpretation of a patient's genetic metabolism can potentially provide tailored drug therapy or personalized medicine which ideally would lead to maximizing therapeutic effect in a more timely manner with dosing specific to the patients inherent metabolism [18]. Currently, there exists testing that helps to optimize the treatment of many diseases including cardiovascular disease, Alzheimers, cancer, HIV, asthma, and mental health [17]. In HIV medicine, routine testing is now done for a genetic variant that makes patients more prone to side effects from the drug abacavir (Ziagen) [6]. Oncologists test for tumor expression of the HER2 protein for targeted treatment with trastuzumab (Herceptin) [6]. The FDA now also recommends genetic testing for the chemotherapy drug mercaptopurine (Purinethol) in patients with acute lymphoblastic leukemia since some people possess a genetic variant that interferes with the metabolism of the drug leading to severe side effects [6]. The presence of certain SNPs can also impact the metabolism of warfarin (Coumadin) and clopidogrel (Plavix) which is a class of polymorphisms identified in the cytochrome P450 enzymes that affect drug metabolism. These variations can enhance or diminish metabolism which can result in variable outcomes depending on the active metabolites of the drug [19]. The FDA has now labeled several hundred medications with pharmacogenomic warnings or indications on the labels (see Table 4).

Table 4 Common medications with FDA pharmacogenomic labels

Psychiatry medications: amitriptyline (Elavil), aripiprazole (Abilify), citalopram (Celexa), diazepam (Valium), fluoxetine (Prozac), paroxetine (Paxil), risperidone (Risperdal), venlafaxine (Effexor)
Analgesics: tramadol (Ultram), codeine
Cardiology: carvedilol (Coreg), clopidogrel (Plavix), isosorbide (Imdur), hydralazine, metoprolol (Lopressor, Toprol), propranolol (Inderall), warfarin (Coumadin, Jantoven)
Gastroenterology: dexlansoprozole (Dexilant, Kapidex), pantoprazole (Protonix), omeprazole (Prilosec), esomeprazole (Nexium), lansoprazole (Prevacid)
Infectious disease: nitrofurantoin (Macrobid, Macrodantin,Furadantin), terbinafine (Lamisil), rifampin (Rifadin, Rimactane), sulfamethoxazole (Bactrim)
Neurology: carbamazepine (Tegretol), galantamine (Razadyne), phenytoin (Dilantin), valproic acid (Depakote, Depakene, Depakon, Stavzor)

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 then 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 [20]. 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 5).

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 it 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 [21]. 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 [22]. 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 this is why genetically identical twins are not fully phenotypically identical [22]. This epigenetic modification can be part of normal cellular processes, such as X-inactivation [23].

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 [23]. Interaction with the environment including naturally occurring and man made compounds

Table 5 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

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 [24]. 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 psychosocial impact of these results [25]. 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 [25].

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, 26, 27].

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, 28, 29]. 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

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Contents

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Newborn Resuscitation

Term infants who appear well at delivery and have clear amniotic fluid and good respiratory effort as well as muscle tone may receive routine newborn care. This includes providing warmth, clearing of the airway if needed, drying and stimulating of the infant, and ongoing assessment of the infant's color as they transition to extrauterine life. These babies may remain with their mothers during and after this time [1].

Infants who do not meet the criteria for routine newborn care require more intervention. This may include not only initial stabilization but also ventilation, chest compressions, and emergency medications.

All health-care providers that are involved in the delivery of newborns should be skilled in neonatal resuscitation. In about 10 % of all deliveries, the transition from fetus to newborn will require intervention by a skilled provider or team. One of the most highly respected sources of information available on the training, skills, and procedures needed for delivery room stabilization is the Neonatal Resuscitation Program (NRP). Completion of the NRP program should be considered by all hospital personnel who may be involved in the stabilization and resuscitation of neonates.

The delivery room should be equipped with equipment that is appropriately sized to resuscitate infants of all gestational ages and sizes. This includes a radiant warmer, a source of oxygen

with an oxygen blender, instruments for intubation as well as for establishing intravenous access, a source for regulated suction, trays equipped for emergency procedures such as umbilical line placement, and drugs that may be needed in resuscitation.

Basic resuscitation skills for a depressed newborn include (1) controlling the thermal environment with the use of a radiant warmer and drying of the infant, (2) positioning and clearing the airway and gentle tactile stimulation, and (3) providing positive-pressure ventilation for newborns with apnea and a heart rate of less than 100. More extensive resuscitation for infants not responding to efforts include (1) administration of chest compressions when the heart rate remains below 60 bpm, despite 30 s of effect positive-pressure ventilation; (2) endotracheal intubation for infants not responding or requiring more prolonged positive-pressure ventilation; (3) central circulation access through the umbilical venous catheter; and (4) administration of emergency medications such as epinephrine through the endotracheal tube or preferentially the umbilical vein [1].

Stabilization for Transfer to the Nursery or Transport to Intensive Care

Postresuscitation priorities include assessment for emergent anomalies, maintenance of basic needs, effective communication with and support of the family, and decisions about the level of care required. Pulse oximetry and a cardiorespiratory monitor are used to monitor ongoing success. Oxygen saturations should be kept at 88–92 % for preterm newborns and 9–100 % for term newborns. Baseline tests for unstable newborns include a chest radiograph, complete blood count (CBC), glucose, and blood gases (arterial if possible). A sepsis workup and other laboratory tests may also be considered. Ventilatory support is needed for persistent respiratory distress, apnea, or deteriorating blood gases (especially Pco2>60 with acidosis). Until respiratory status stabilizes, intravenous fluids are started with 10 % dextrose in water (D10W) at 60 ml/kg/day for term infants in the first 24 h of life. Timely transport of unstable or high-risk neonates for tertiary care enhances outcome [1].

Giving Bad New to Parents After Delivery

Family physicians will confront situations where they need to discuss bad news with parents regarding their newborn. These situations can range from a stillbirth to a neonatal death, to a serious anomaly, or an isolated problem such as cleft palate. Studies have surveyed patients and family members to determine how they believe physicians should give bad news. These studies have covered a wide range of patient and family experiences including cancer, birth defects, traumatic injury, death, etc. Four common themes emerge from this work and indicate that patients want (1) a clear, direct statement of the news, (2) time to talk together in private, (3) openness to emotion, and (4) ongoing involvement in decision making [2]. In addition, when physicians are discussing bad news with parents regarding a newborn, parents prefer that the physician talk to both parents together and early. Parents also prefer that the physician, when possible, discuss the news with the baby present and being held by a parent or the physician [1].

Common Problems in the Nursery

Late Preterm Infants

Late preterm infants are born at a gestation age between 34 and 36-6/7 weeks. These infants should not be considered “near term” as developmental and physiologic immaturity leads to a higher morbidity and mortality rate than term infants. These babies are more likely to have issues with respiratory distress, apnea, temperature instability, hypoglycemia, jaundice, and feeding difficulties. Physicians who care for these infants need to be aware that these infants are at increased risk both during their hospital stay and after discharge. Due to higher rates of hospital readmissions than term infants, there are now

recommended criteria for discharge. These include (1) 24 h of successful feeding, (2) weight loss less than 7 %, (3) formal evaluation of breastfeeding, (4) passing a car seat trial, and (5) an established discharge feeding plan [2, 3].

Term infants who are appropriate for gestational age have birth weights between 2500 and 3999 g [4].

Small for Gestational Age

A neonate termed small for gestational age refers to a birth weight below the 10th percentile for gestational age [4]. They may have either symmetric or asymmetric fetal growth restriction; symmetric FGR have reductions in both body and head growth. Symmetric FGR begin early in gestation due to an intrinsic etiology such as congenital infections, chromosomal abnormalities, or decreased nutrient supply early in development. Infants with asymmetric FGR have a relatively normal length and head growth but reduced body weight. This usually begins in the late second and third trimester, and the etiology is often less clear. Possible reasons include reductions in fetal nutrients that limit glycogen and fat storage, yet allow continued brain growth. However, in about 70 % of cases, no cause can be identified. SGA infants should be monitored closely for hypoglycemia, polycythemia, as well as temperature instability [4].

Large for Gestational Age

Large for gestational age babies are defined as a birth weight greater than the 90th percentile for gestational age [4]. Macrosomia refers to excessive intrauterine growth beyond a specific threshold, regardless of the infant's gestational age, and is usually defined as a birth weight greater than 4000 g or 4500 g.

The etiology of this condition may be due to (1) various genetic and intrauterine environmental factors including a familial trait (e.g., mothers who were LGA are more likely to deliver an infant who is LGA) and (2) maternal factors including maternal diabetes and excessive maternal weight gain. These infants are at higher risk for birth injury, respiratory distress, hypoglycemia, and polycythemia [4].

Neonatal Sepsis

Neonatal sepsis is typically classified into "early onset" sepsis (neonates less than 3 days old) and "late onset," occurring beyond 3 days of age.

Sepsis is often accompanied by nonspecific signs and symptoms, making early detection difficult; 2 in 1000 neonates have bacterial sepsis. The risk increases with preterm labor, premature rupture of membranes (greater than 18 h), or intrapartum fever. The etiology of early onset sepsis is transmission from mother to baby during the course of labor and delivery. The organisms commonly causing early onset infection include group B streptococcus (GBS), *Escherichia coli*, and *Listeria monocytogenes*. The implementation of prenatal screening and GBS treatment protocols have resulted in decreasing prevalence of GBS sepsis [5, 6].

The onset of early sepsis is most rapid in infants born prematurely; however, 85 % will present in 24 h, 5 % present in 24–48 h, and an even smaller percentage present in 48–72 h of age [5, 6]. The clinical diagnosis of sepsis in the neonate is difficult because the signs of sepsis are nonspecific and can be observed with other conditions that are not related to infection. Early manifestations include temperature instability, lethargy, and poor feeding. The physician must have a high index of suspicion for sepsis and carefully observe for subtle signs in order to detect this potentially devastating condition as soon as possible.

Diagnosis

Helpful studies include CBC, blood cultures, and C-reactive protein (CRP) values. Urine cultures are not routinely obtained as part of the sepsis workup in a neonate less than a few days old. Lumbar puncture should be performed as part of the sepsis workup for those whose clinical course suggests sepsis or meningitis. Mortality from untreated sepsis can be as high as 50 %, so treatment is initiated while awaiting culture results. Figure 1 demonstrates a suggested protocol for initial diagnosis and management of sepsis in newborns.

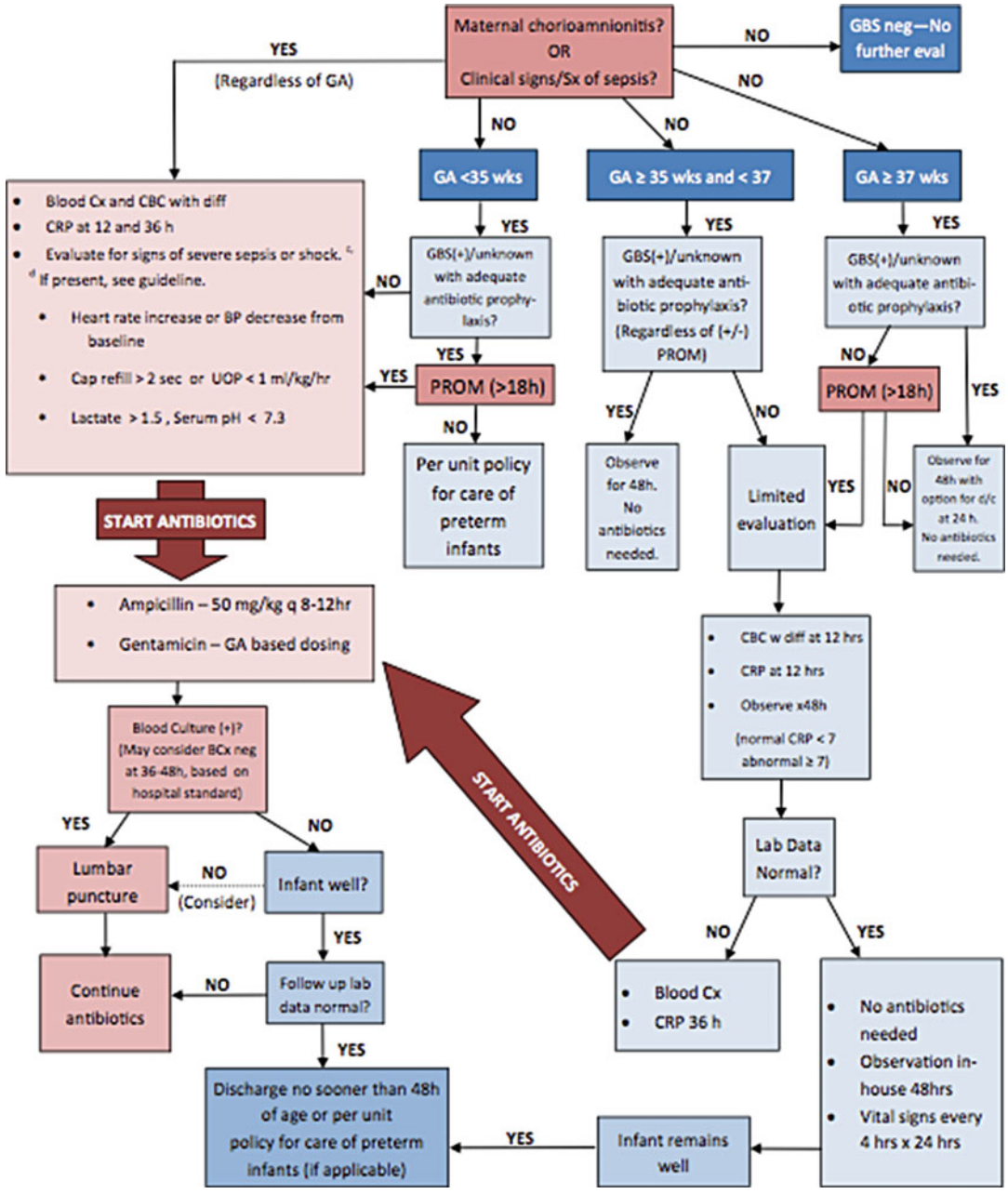

Fig. 1 Suggested protocol for management of suspected sepsis in term and preterm newborns

Treatment

The optimal treatment of infants with suspected early onset sepsis is broad-spectrum antimicrobial agents (ampicillin and an aminoglycoside). Once the pathogen has been identified, antimicrobial therapy should be narrowed, unless synergism of multiple antibiotics is required. Typically, ampicillin is used with dosing of 50 mg/kg/dose given every 8 h and gentamicin with dosing of 4 mg/kg/dose given every 24 h. The results of blood cultures, CRP values, and clinical course will guide the duration of antibiotic therapy; antimicrobial

therapy should be discontinued at 48 h in patients with negative cultures. Bacteremia is treated for 10 days and meningitis requires at least 14 days of therapy depending on the response and causative organism [5, 6].

The addition of acyclovir to the antibiotic regimen should be considered if there is suspicion for herpetic infection.

Respiratory Distress

Tachypnea, grunting, nasal flaring, retractions, and cyanosis are manifestations of respiratory distress. In neonates, this may be transient; however, if these symptoms persist, a diagnostic and therapeutic evaluation should be pursued. In newborns, differential diagnosis includes sepsis, transient tachypnea of the newborn (TTN), respiratory distress syndrome (RDS), persistent pulmonary hypertension (PPHN), pneumonia, pneumothorax, congenital heart disease, and more rare congenital defects including congenital diaphragmatic hernia [7, 8].

Transient tachypnea of the newborn presents within 2 h of birth and frequently resolves within 24 h; not uncommonly, it may persist for up to 72 h. Tachypnea (respiratory rate greater than 60), little hypoxia or hypercarbia, and radiographic findings of perihilar streaking and/or fluid in the fissures are common. Oxygen requirements gradually decrease after the first few hours. If the course is atypical or there is a risk of sepsis, neonatal pneumonia and other causes must be considered [7, 8].

Respiratory distress syndrome (RDS) is caused by a deficiency of surfactant, the phospholipids that reduce alveolar surface tension and maintain alveolar stability. RDS is more common in preterm infants, who can exhibit hypercarbia, hypoxia, and a "ground-glass" appearance on x-ray with air bronchograms.

Persistent pulmonary hypertension usually occurs in term infants and is characterized by tachypnea and cyanosis. A common finding is a significant difference in pre(right hand)- and post-ductal (foot) saturation. Transfer to a tertiary care center for further management is recommended in these infants.

Jaundice

Elevated bilirubin levels are seen in the majority of neonates in the first few days of life, due to increased production and decreased clearance of bilirubin. This condition is known as "physiologic jaundice." Conditions that aggravate this physiologic hyperbilirubinemia include inborn errors of metabolism, ABO incompatibility, hemoglobin variants, and conditions such as sepsis. It is important to distinguish "physiologic" from "exaggerated physiologic" and "pathological" forms of hyperbilirubinemia. "Pathological hyperbilirubinemia" is a medical emergency.

Neonatal hyperbilirubinemia appears to be more common among Asian and Native American newborns than those of Black or Caucasian ethnicity [9].

One of the main goals of screening for and treating pathological hyperbilirubinemia is the prevention of neurologic sequelae. "Acute bilirubin encephalopathy" describes acute manifestations of bilirubin toxicity in the first few weeks of life, including lethargy and hypotonia and progressing to apnea, fever, coma, seizures, and death. "Kernicterus" refers to the chronic and permanent sequelae of bilirubin toxicity for newborns that survive, including cerebral palsy, auditory dysfunction, dental dysplasia, and paralysis of upward gaze [10].

Primary Prevention

Since poor caloric intake and dehydration are associated with hyperbilirubinemia, clinicians should advise breastfeeding mothers to nurse their newborns at least 8–12 times daily during the first week of life. Routine supplementation of liquids other than breast milk should be discouraged in infants who are not dehydrated.

Secondary Prevention

It is advised that all pregnant women be tested for ABO and Rh (D) blood types and undergo serum screening for isoimmune antibodies. For Rh-negative mothers and those without prenatal blood group testing, the infant cord blood should be tested for ABO and Rh (D) typing, and a direct antibody (or Coombs' test) should be performed.

Table 1 Risk factors for development of severe jaundice in term infants

Major risks for development of significant jaundice
ABO or other blood group incompatibility with positive Coombs' test
Gestational age 35–36 weeks
East Asian race
Newborn with sibling who received phototherapy
Cephalhematoma or significant bruising
Minor risks for development of significant jaundice
Predischarge TSB or TcB in the high intermediate risk zone
Gestational age 37–38 weeks
Male gender
Jaundice observed before discharge

Info from Refs. [10, 11, 14]

Screening and Assessment

Maternal-child hospital units should have established protocols to routinely monitor all newborns for the development of jaundice. Clinical assessment for jaundice should occur at least every 8–12 h. Jaundice is usually first seen in the face and progresses to the trunk and extremities, but assessment by physical examination alone may not be sufficiently sensitive or specific, especially for darkly pigmented infants [11].

A total serum bilirubin (TSB) study should be drawn for every newborn with clinical jaundice in the first 24 h of life. A transcutaneous bilirubin (TcB) or TSB should also be performed on all infants in whom there appears to be clinical jaundice that is excessive for the infant's age. The American Academy of Pediatrics recommends that all infants be screened for jaundice before hospital discharge by either assessment of clinical risk factors or a TcB or TSB level [10]. Risk factors for the development of severe hyperbilirubinemia are listed in Table 1. All parents should be given information about jaundice and how to monitor for it after discharge, and all infants should be examined by a health professional within the first few day of discharge. This should include an assessment of weight, intake, and output as well as jaundice [10].

Laboratory Assessment

All bilirubin levels should be interpreted based upon the infant's age in hours, and the need for phototherapy should be based on the zone in which the TSB falls. See Table 2 for recommendations on laboratory studies based upon risk factors. Standard curves for risk stratification have been developed by the American Academy of Pediatrics [10].

Table 2 Laboratory evaluation for jaundice in infants 35 weeks or greater

Clinical finding	Laboratory evaluation
Jaundice in the first 24 h of life	Check TSB
Newborn on phototherapy or with bilirubin rising rapidly (crossing percentiles on curve)	Maternal and infant blood types, Coombs' test, complete blood count with reticulocyte count, and peripheral smear; consider G6PD
	Repeat TSB every 4–24 h, depending on level and likely etiology
TSB level approaching exchange transfusion levels and/or not responsive to phototherapy	Check reticulocyte count, G6PD, albumin
	Check phototherapy unit output; consider increasing intensity with additional overhead phototherapy lights and/or bili blanket
Elevated direct (conjugated) bilirubin	Check urinalysis and culture; consider sepsis evaluation; consider evaluation for congenital viral infection, anatomic abnormalities (biliary atresia, cholodochal cyst) – viral cultures, abdominal ultrasound
Jaundice at or beyond week 3 of life	Check total and direct bilirubin, evaluate for cholestasis if direct elevated, check thyroid and galactosemia screens

Info from Refs. [10, 11, 14]

For any infant requiring phototherapy or for those in whom a suspicion for pathological hyperbilirubinemia exists, appropriate investigations should be carried out. These infants should undergo measurement of total and direct (conjugated) bilirubin to evaluate for cholestasis, as well as a Coombs' test and other testing as appropriate. This may include testing for galactosemia and thyroid problems. If the

direct bilirubin is elevated, further investigation for causes of cholestasis should be undertaken. The glucose-6-phosphate dehydrogenase (G6PD) level should be measured for infants receiving phototherapy whose response to phototherapy is poor or whose family history or ethnic origin suggests risks for G6PD deficiency [10].

Treatment

Decisions to initiate treatment should be made based upon the American Academy of Pediatrics standardized algorithm [10]. If the TSB rises to a level necessitating exchange transfusion or if the TSB is 25 mg/dl or higher, the infant must be immediately admitted to a hospital for exchange transfusion. Exchange transfusions should only be performed by trained personnel in a neonatal intensive care unit. Immediate exchange transfusion should be initiated for any infant with jaundice and signs of intermediate to advanced acute bilirubin encephalopathy: hypertonia, arching, retrocollis, opisthotonos, fever, or high-pitched cry [12].

When initiating phototherapy, precautions include assuring adequate fluid intake, patching eyes, and monitoring temperature. A transient rash, green stools, and irritability may occur. Phototherapy may generally be stopped when the TSB falls by 5 mg/dl or below 14 mg/dl. A rebound rise is uncommon in newborns with initial suboptimal feeding that has improved, but more common in those with blood group incompatibilities. Home phototherapy for uncomplicated jaundice (using a fiber-optic blanket) in carefully selected newborns with reliable parents allows continued breastfeeding and bonding with the family.

Breastfeeding is often associated with higher bilirubin levels than those seen in exclusively formula-fed infants. More frequent feeding usually reduces bilirubin levels. "Breast milk jaundice" is a delayed but common form of jaundice that is usually diagnosed in the second week of life and peaks by the end of the second week, gradually resolving over 1–4 months. If evaluation reveals no pathologic source, breastfeeding can generally be continued, although supplementation may be required to ensure adequate hydration. Temporary discontinuation of breastfeeding for diagnosis or other reasons increases the risk of breastfeeding failure and is usually unnecessary [13]. Assessment of newborns for adequate feeding and hydration is reviewed in Table 3.

Table 3 Assessment of newborn feeding and weight gain

Maternal factors
Has the mother experienced engorgement?
Do the breasts feel softer after feedings?
Are there risk factors for delayed lactogenesis? (Cesarean delivery, maternal obesity, LGA, prolonged second stage labor, flat or inverted nipples)
Does latch occur without difficulty, pain, or pinching?
Are there signs of milk ejection reflex? (Breast tingling, uterine cramping, dry mouth)
Newborn factors
Does the newborn feed at least 8–12 times daily?
Does the newborn complete feedings in 15–45 min?
Does the baby self-detach from breast after most feedings?
Is there an audible swallow with feedings?
Has the baby lost more than 8–10 % of birth weight?
Has the baby returned to birth weight by the 14th day of life?

Information from Refs. [13, 31, 32]

Hypoglycemia

Hypoglycemia can occur with or without risk factors or symptoms and is more common in preterm, small for gestational age, and large for gestational age newborns, as well as those born to mothers with gestational diabetes and/or obesity [14]. The most common signs are "jitteriness," hypothermia, poor feeding, abnormal cry, hypotonia, and seizures [13]. Treatment for the asymptomatic infant is debated, but most sources agree that infants with an initial blood glucose (BG) less that 25 mg/dl within the first 4 h of life should be treated, as well as those who are symptomatic [15–17]. Prolonged or several hypoglycemia may result in long-term neurologic sequelae and childhood metabolic syndrome [18, 19]. A proposed algorithm for treatment can be found in

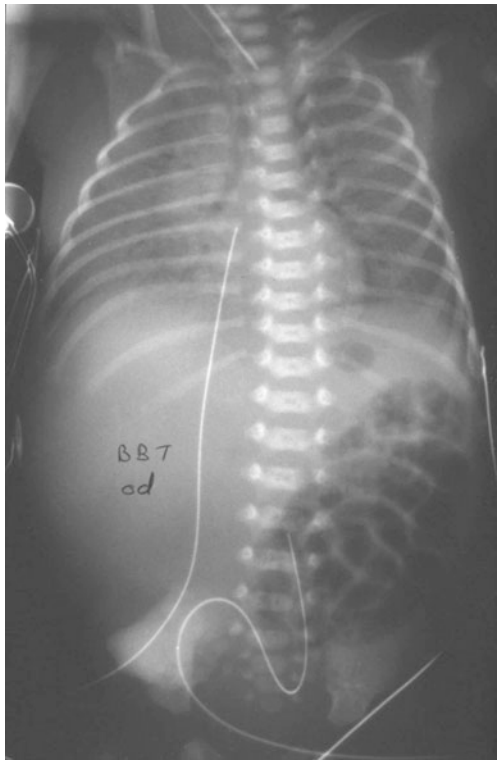

Fig. 2 RDS with sever features. An endotracheal tube is in place

Fig. 2. An initial attempt at feeding should occur (preferably breast or formula if maternal choice) in the first hour of life before a BG is checked [14].

Metabolic Disorders

Unexplained poor feeding, vomiting, lethargy, seizures, or coma in a previously healthy newborn in the first few hours to weeks of life may suggest an inborn error of metabolism. After excluding conditions such as sepsis and hypocalcemia, plasma levels of ammonia, bicarbonate, lactate, and pH should be measured. Early consultation and treatment can avoid severe metabolic and neurologic complications. Each state in the United States has enacted legislation for mandated screening of newborns for certain hereditary metabolic disorders. The exact conditions screened for, however, vary from state to state, and the results of serum screening are often not available for 3–4 weeks.

Anemia

The World Health Organization recommends late clamping of the umbilical cord (1–3 min after birth) to maximize perfusion to the neonate, unless immediate resuscitation is required [20]. This approach can help prevent anemia, with a more substantial benefit for preterm newborns. In newborns delivered after 34 weeks, a central venous hematocrit less than 45 % is often caused by blood loss and less often by hemolysis or congenital anemias. Further evaluation should include review of prenatal history, physical examination, red blood cell indices, and a peripheral smear. A Coombs' test, reticulocyte count, and Kleihauer-Betke stain of maternal blood (to assess for fetomaternal transfusion) may be necessary. If the hematocrit is more than 20 % and the newborn is hemodynamically stable, observation is generally indicated. Severe hemolysis may require exchange transfusion.

Polycythemia

A venous hematocrit of more than 65 % or a capillary hematocrit of more than 70 % may cause plethora, hyperviscosity, and jaundice. Signs and symptoms may include lethargy, respiratory distress, irritability, seizures, feeding difficulties, cyanosis, and hypoglycemia. If the infant is symptomatic and hematocrit elevation is confirmed, a partial exchange transfusion may be considered to lower the hematocrit to 50 %.

Birth Injuries

Caput succedaneum (soft tissue swelling of the scalp that crosses suture lines) usually results from vertex vaginal delivery but may also be seen with cesarean deliveries. It is benign and resolves over the first few weeks of life. *Cephalhematoma* is a slow subperiosteal hemorrhage limited to the surface of one cranial bone and does not suture lines. It is much more common with assisted vaginal birth (incidence with vacuum higher than with forceps) and resolves spontaneously but may be

associated with jaundice as the blood collection dissipates [21]. *Subgaleal hemorrhage* occurs when blood accumulates in the space between the periosteum of the skull and the aponeurosis, with the potential for massive blood loss as blood accumulates in the subgaleal space. Although rare, mortality is high unless rapid volume resuscitation is initiated. Surgical evacuation is rarely needed [22]. *Intracranial hemorrhage* is usually associated with preterm delivery but may occur in term infants. Risk is increased with operative delivery. Close monitoring is required due to risk of extension of the hemorrhage into surrounding tissue and the potential for post-hemorrhagic hydrocephalus [23].

Clavicle fractures are most commonly associated with shoulder dystocia and/or birth weights more than 4 kg. Nondisplaced fractures are often asymptomatic until a palpable callus forms in days to weeks. Displaced fractures are more likely to be accompanied by findings immediately post delivery, including crepitus, edema, crying with passive motion, and lack of movement (pseudoparalysis) in the affected arm. Diagnosis is made by plain radiography and requires investigation for accompanying brachial plexus injury. Most clavicle fractures heal spontaneously with no long-term sequelae. Analgesics may be given for pain. Also for comfort, the arm on the affected side can be place in a long-sleeved garment and the sleeve pinned to the chest, with the elbow flexed at 90°. Callus formation and lack of tenderness on exam are usually sufficient to document healing, but some clinicians advocate for radiography at 2 weeks [24].

Brachial plexus injury generally occurs with shoulder dystocia and clavicle fracture but may be seen in atraumatic deliveries. Upper plexus injury involving C5 and C6 manifests as adduction and internal rotation of the arm and forearm extension, with preserved and wrist movement. When C7 is also involved (Erb palsy), there is also flexion of the wrists and fingers. Total brachial plexus palsy (C5 to T1) presents with arm paralysis and is occasionally accompanied by a Horner syndrome [25].

Management of newborn brachial plexus injury is controversial. Physical therapy and observation for recovery is often sufficient. Surgical evaluation and possibly intervention are usually recommended when functional recovery does not occur in 3–9 months [25].

Human Immunodeficiency Virus (HIV) Infection in Newborns and Infants

In 2010, an estimated 217 children under the age of 13 years were diagnosed with HIV in the United States, and 162 (75 %) of those children were perinatally infected. Despite an overall increase in the number of HIV-infected people giving birth, since the mid-1990s, interventions have resulted in more than a 90 % decline in the number of perinatally acquired HIV infections in the United States. Despite these encouraging results, HIV disproportionately affects black/African American children [26].

In 1994, the AIDS Clinical Trials Group (ACTG) Protocol 076 demonstrated that if previously untreated HIV-infected pregnant women are treated with zidovudine (ZDV), the risk of vertical transmission can be reduced by two thirds. Protocol 076 involved started pregnant women on oral ZDV as early as 14 weeks' gestation and continuing until labor, with conversion to intravenous ZDV infusion during labor. Neonates were then treated with oral ZDV for the first 6 weeks of life [27].

Since 1994, additional research has demonstrated that mother-to-child transmission can be reduced to less than 1 % when HIV infection is diagnosed before or during pregnancy, and appropriate protocols are followed. The CDC continues to recommend intravenous zidovudine during labor and neonatal prophylaxis, but currently recommends that pregnant women be offered highly active antiretroviral therapy (HAART) regimens during pregnancy, starting by 12 weeks' gestation. Universal HIV screening for all pregnant women is thus recommended, as early in pregnancy as possible. Previously untested women who present in labor should undergo rapid HIV testing, with subsequent testing for the newborn [28].

For women with a known prepregnancy HIV-positive serostatus, many HAART regimens

can and should be continued throughout pregnancy, but clinicians should refer to the CDC website for frequently updated guidelines on the use of the multidrug regimens. For HIV-infected pregnant women with HIV viral loads (HIV RNA) greater than 1000 copies/ml3, cesarean delivery is recommended. In the United States and other developed countries, in which the protective effect of breastfeeding does not outweigh the risk of transmission, breastfeeding is not recommended for HIV-infected women; their newborns should receive either donor breast milk from a certified milk bank or formula feedings [28].

Because approximately 18 % of all people with HIV do not know their HIV status, many women who are infected with HIV may not know they are infected. The Centers for Disease Control and Prevention (CDC) recommends routine, opt-out HIV testing for all persons aged 13–64 years in health-care settings, including women during every pregnancy [29].

Infant Diagnosis and Treatment

Newborns and infants with HIV infection must be quickly identified and started on HAART to improve long-term outcomes and prevent opportunistic infections. The physical examination is often normal in newborns. Presenting symptoms may be subtle but can include: failure to thrive, lymphadenopathy, hepatosplenomegaly, recurrent diarrhea, pneumonia, and persistent candidal infections.

Any infant with the above symptoms, other signs of immunocompromise, or born to a known HIV-infected mother should be tested. Initial testing should include a standard HIV screening (Western blot) test as in adult patients as well as an HIV viral load (quantitative HIV RNA), since the Western blot may not be positive with acute infection. For infants born to HIV-infected mothers, if initial newborn testing is negative, follow-up test should occur at 2 weeks, 1–2 months, and 3–6 months [28].

Where possible, treatment of newborns with HIV infection should be initiated in conjunction with a consultant with expertise in neonatal HIV management.

Approaches to Common Neonatal Anomalies

Table 4 provides a brief overview of common anomalies encountered by those caring for newborns.

Guidelines for Early Hospital Discharge of the Newborn

The newborn hospital stay should be long enough to allow identification of early problems and to assure that the family is prepared for the infant's transition to home. Many of the most concerning cardiopulmonary problems become apparent in the first 12 h after birth. Detection of significant jaundice, ductus arteriosus-dependent cardiac anomalies, gastrointestinal obstruction, and certain other issues may require a longer period of observation by skilled health professionals.

A 48-h stay after vaginal delivery and a 96-h stay after cesarean delivery are generally recommended and may help avoid readmissions [30]. Discharge after a shorter length of stay for term infants, especially those born between 39 and 42 weeks gestation, may be considered if a number of criteria are met. These include: a negative prenatal maternal group B streptococcus screen, normal clinical course and physical examination at discharge, stable vital signs for 12 h prior to discharge, regular urination and passage of at least one stool, and successful completion of two consecutive feedings; clinical risk for hyperbilirubinemia has been assessed; maternal laboratory screen results have been reviewed (especially HIV, hepatitis B, blood type, and syphilis screens); hepatitis B vaccine has been administered; metabolic and hearing screens have been completed; home safety and social support has been assessed; and a medical home for follow-up care has been identified.

Newborns discharged at less than 24 h of age will need to have state-mandated newborn metabolic screening repeated. Newborns being discharged less than 48 h after delivery should generally be seen by a health professional (either home or office visit) within 48 h of discharge.

Table 4 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 and possible renal abnormalities
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

(*continued*)

Table 4 (continued)

Abnormality	Causes	Evaluation/treatment
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
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 2 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

(*continued*)

Table 4 (continued)

Abnormality	Causes	Evaluation/treatment
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
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 gastrograffin enema (successful in two thirds), otherwise surgery; consider referral to a pediatric pulmonologist, check sweat chloride test at approximately 3 months of age
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

(*continued*)

Table 4 (continued)

Abnormality	Causes	Evaluation/treatment
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 ultasonography and surgery
Musculoskeletal		
Syndactyly (fusion of two or more digits)	Sporadic or autosomal dominant with varying expressivity	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 % to 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)
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

Infant Care

Well-Child Care

Well-infant visits should emphasize anticipatory guidance and answering parental questions about infant health during the period of rapid transitions. Cultural and socioeconomic issues, family expectations and stressors, and an assessment of the infant's physical environment should be addressed – preferably starting with prenatal care. Each visit should include an age-appropriate physical examination and developmental assessment as well as pertinent immunizations and screening tests. After an initial clinician visit within the first 4 days of life as noted above, newborns should be seen again at 1–2 weeks, then 1 month, 2 months, 4 months, and 6 months of life. Additional visit schedules and guidelines for well-infant visits are covered in greater detail in chapter "► Clinical Prevention".

Nutrition and Feeding

Breast Milk

The American Academy of Family Physicians and American Academy of Pediatrics recommend that most infants be exclusively breastfed for the first 6 months of life and continue some breastfeeding for at least 12 months [31, 32]. Infant feeding is a personal and family choice, but in the absence of medical contraindications to breastfeeding, physicians should provide up-to-date information to expectant parents regarding the risks and benefits of feeding choices.

Breastfeeding optimizes newborn immune system development and disease prevention and assists with maternal postpartum weight loss and psychologic well-being. Exclusively or primarily formula-fed newborns are at increased risk for: gastrointestinal, ear, and respiratory infections throughout infancy and childhood, type 1 diabetes, asthma, childhood and adult obesity, and leukemia. Mothers who primarily feed their newborns formula increase their own risks for obesity, diabetes, ovarian and breast cancer, and depression [31, 32].

Evidence-based studies indicate that maternal education regarding the benefits of breastfeeding should begin early in prenatal care and include physician counseling as well as structured breastfeeding classes or prenatal groups. Women with a history of breast surgery or flat or inverted nipples may visit a trained lactation consultant for support during their pregnancy to help prevent or ameliorate breastfeeding difficulties [13].

During intrapartum care, physicians should seek to minimize the use of unnecessary medical interventions, as many medications and interventions utilized during labor can decrease milk supply or otherwise negatively impact breastfeeding. Every effort should be made to support immediate and prolonged maternal-newborn skin to skin contact (provided the newborn is medically stable at birth), latch and breastfeeding within the first hour of life, and "rooming in" during the hospital stay with minimal mother-newborn separation. A pacifier should not be given to breastfeeding infants during the first several weeks of life until breastfeeding is well established. Liquids other than colostrum or breast milk should not be given unless there is a documented medical need, such as weight or feeding difficulty. If the newborn experiences early latch difficulties, supplementation with expressed breast milk is preferable to supplementation with formula. Assistance from a trained lactation consultant is a key element in the support of breastfeeding dyads [13].

There are very few absolute contraindications to breastfeeding. These include maternal HIV infection and a newborn diagnosis of galactosemia. Certain medications pass through breast milk – updated guides to medications can be found at the National Institutes of Health LactMed website [33]. In many cases, if a maternal medication is not compatible with breastfeeding, the family physician could consider substituting an alternate medication that is compatible.

Vitamin D Supplementation

All newborns should consume 400 IU/day of vitamin D to prevent vitamin D deficiency and associated abnormalities of calcium metabolism that may occur, including rickets. Deficiencies of vitamin D have also been linked to a number of conditions, including developmental delay, and

possibly type 1 diabetes or cardiovascular disease later in life [34]. Newborns that are exclusively breastfed and newborns consuming less than 1 l of formula daily should be prescribed an oral vitamin D supplement containing 400 IU daily. In the first month of life, few newborns that are fully formula fed will consume a full liter daily; these newborns should also be prescribed vitamin D for at least 1 month.

Formula

If formula feeding is chosen, the majority of infants tolerate cow's milk-based formulas. For healthy term infants, differences between brands of formula are generally insignificant. True infant intolerance to cow's milk-based formulas is unusual. Soy protein formulas are of value only if lactose intolerance is strongly suspected, such as after prolonged episodes of loose stools. Even then, the intolerance is usually transient and cow's milk-based formula can be tried again in 2–4 weeks.

Because formulas do not contain fluoride, physicians should suggest that parents mix the powdered forms with fluoridated water. Low iron formulas offer no advantage; their use will result in iron deficiency anemia in most infants.

Advancing Infant Diet

Infants should continue breast milk or formula until 12 months of life because introducing cow's milk before this age increases the risk of occult gastrointestinal bleeding and iron deficiency anemia. At 12 months, the child can generally start whole or 2 % milk and switch to skim milk at 2–3 years of age.

Introducing nonmilk foods before 6 months of life is generally not beneficial and may increase risks of food allergies and obesity – although findings in the scientific literature are controversial [32, 35]. Some generally accepted guidelines for introducing nonmilk foods include:

1. Separate the introduction of new foods by 2–3 days to more easily determine the cause of any food intolerance.
2. Start with easily digested fruits and vegetables, such as yellow vegetables, avocados, and sweet potatoes.
3. Postpone potential allergens such as citrus fruits, wheat, and eggs until 9–12 months of age.
4. Minimize the risk of airway obstruction by avoiding spongy foods (e.g., hot dogs and grapes) and foods with kernels (e.g., corn and nuts).

Treatment of Colic

All infants, whether they are described as having colic or not, will cry more in the first 3 months of life than any other time. Colic is broadly defined as crying for no apparent reason that lasts greater than 3 h/day and occurs on more than 3 days a week in an otherwise healthy infant less than 3 months of age [36].

The incidence of colic does not seem to differ between breast- and formula-fed babies, term and preterm, or male and female. Etiology is unknown, although there is probably a combination of factors that contribute to it.

A principal focus is on reassuring parents that the process is a common, self-limited one and providing them with some basic measures to try. These include providing motion as in a mechanical swing, rocker, or front infant carrier or exposure to a steady hum such as in a car or a vacuum cleaner, bundling, and burping well and frequently during and after feeding. Often the physician's most important roles are providing support over time and legitimizing the parents' sense of frustration, and even anger, with the situation. The physician should also encourage parents to help each other with caring for the infant and whenever possible to enlist the help of others so that they have an opportunity to take a break. When all else fails, parents may need permission to periodically shut the door and let the infant "cry it out."

Infants with more prolonged, severe bouts of crying, especially if intermittent throughout the day, may have a remediable organic cause. Constipation should be treated as it would in other infants. Frequent vomiting, especially if accompanied with poor feeding, suggests gastroesophageal reflux. If a trial of medication is not effective, further workup is indicated. With signs of allergy

(eczema, asthma) or a strong family history of allergies, milk allergy should be considered. Finally, although anticholinergic agents have been advocated in the past, their efficacy probably has more to do with their sedating effect than any specific effect on the gastrointestinal muscles. Because they have a potential for severe side effects, they are now considered contraindicated.

Failure to Thrive

The diagnosis of failure to thrive (FTT) is based on growth parameters that (1) fall over 2 or more percentiles (2) are persistently below the 3rd percentile or (3) are less than the 80th percentile of median weight for height measurement. A thorough history and physical examination detect most organic, behavioral, family, and environmental problems that contribute to FTT. This initial assessment should include (1) prior records including growth charts and prenatal history (prematurity, growth restriction), (2) nutrition (diet, behavior), (3) development (cognitive, motor, behavioral, emotional), (4) social context (parental knowledge, family dysfunction, drug abuse, isolation), and (5) environment (poverty, shelter, toxic exposures to lead or pesticides). Diagnostic studies can follow in a stepwise manner, with step 2 studies chosen based on history, physical exam, and severity:

Step 1: complete blood count, electrolytes, urinalysis, and lead level
Step 2: thyroid, stool (culture, ova and parasites, fat), sweat chloride, tuberculosis, HIV screening, skeletal survey, and renal studies

Patients with severe malnourishment who have had no prior workup or for whom outpatient care has failed may require inpatient care. Collaborative, interdisciplinary treatment involves the parents, physician, social worker, nutritionist, and psychologist. It implements one or more of the following strategies: (1) treating organic factors first, (2) implementing a written nutritional plan for meals and snacks with caloric intake 1.5–2.0 times normal, (3) beginning a vitamin supplement, (4) supporting parents with mealtime observation and coaching, (5) treating specific family problems that interfere with the family's ability to care for the infant (misunderstanding, depression, drug abuse), (5) enlisting social support (family, friends, church), (6) mobilizing community and economic resources for the family, (7) establishing continuity of care and access to the treatment team, and (8) promoting parental competence.

Fever

In children under 3 years of age, if a source for the fever cannot be found, or if otitis media is found, 3–11 % have occult bacteremia. The risk is even higher in infants under the age of 3 months who have an 8.6 % risk of having a serious bacterial infection (27, 28). Although most neonates (younger than 28 days of age) and young infants (29–90 days of age) with fever have a viral illness, the goal of the provider is to identify those children who are at high risk for serious bacterial infection (SBI), requiring empiric antimicrobial therapy and possible hospitalization.

Neonates (0–28 Days)

Available guidelines for fever in young infants do not perform well in newborns less than 28 days of age, and therefore most experts agree that all neonates, regardless of clinical appearance, with a rectal temperature greater than 38 °C or 100.4 °F, have blood, urine, and CSF cultures obtained. Infants should be admitted to the hospital and treated with empiric intravenous antibiotics until cultures are found to be negative, or a full course of treatment is completed.

Ill-Appearing Infants (29–90 Days)

Up to 45 % of ill-appearing young infants may have an SBI and should have blood, urine, and CSF evaluation and empiric antibiotic therapy with admission to the hospital [37, 38].

Well-Appearing Infants (29–60 Days)

Laboratory testing is necessary to help determine which patients are at high risk for a serious bacterial infection. Lab evaluation includes CBC, blood and

urine culture, and CSF cultures in most patients. Some clinicians may elect to perform less of a laboratory evaluation; there are no guidelines for the minimal evaluation of fever in well-appearing infants ages 29–60 days. Many studies have reported, however, that infants who are at low risk of SBI based on history, physical examination, and laboratory tests can be safely managed as outpatients. Follow-up must be arranged within 24 h, either by phone or return visit to the provider. If 24 h follow-up is problematic, for whatever reason, then the infant should be admitted to the hospital. Infants who are followed as outpatients may be treated presumptively with ceftriaxone (50 mg/kg), pending culture results [37, 38].

However, patients should not receive empiric antibiotics unless a full sepsis workup has been done, including obtaining a CSF culture.

Infants 61–90 Days Old

Data regarding the incidence of SBI among infants 61–90 days with fever on which to base definitive guidelines is limited. Since infants less than 3 months of age have not yet been fully immunized against *Haemophilus influenzae* type b and pneumococcus, most experts recommend laboratory analysis including CBC, urinalysis, and blood and urine cultures. A WBC count outside of the normal range of 5000–15,000/microL or band count greater than 1500/microL necessitates the need for CSF culture and treatment with parenteral antimicrobials. Any ill-appearing infant warrants full laboratory evaluation and admission to the hospital for well-appearing patients with normal CSF and urinalysis, IM ceftriaxone (50 mg/kg) is an option. These infants must have follow-up within 24 h either by phone or by visit [38, 39].

Infants 3–36 Months Old

There is no need to screen for occult bacteremia in infants with temperatures <39 °C (102.2 °F). However, infants with persistent fever for more than 2–3 days, worsening clinical appearance, or temperatures >39 °C without an apparent source of the fever other than otitis media, constitute a higher risk group. They should be evaluated with a WBC count. If the count is >15,000/mm^3 or they have a bandemia, a blood culture is indicated, as well as a parenteral antibiotic (Ceftriaxone 50 mg/kg/dose) while the cultures are pending. In addition, a catheterized urine sample should be considered for all boys less than 6 months of age or girls less than 2 years of age [39].

Fever is a common symptom in this age group of children. The majority of children will have a self-limited viral infection or a recognizable source of infection upon physical examination. The introduction of vaccines to prevent *Haemophilus influenzae* type b and pneumococcal disease has been very successful in lowering the incidence of occult bacteremia, and therefore the approach to the child who has a fever without a source is greatly determined by immunization status. Fever of 39 °C or higher is the threshold above which evaluations for a source of occult infection, including UTI, may be warranted [40].

Sudden Infant Death Syndrome

Sudden infant death syndrome (SIDS) is the leading cause of infant mortality between 1 month and 1 year of age in the United States. It is defined as the sudden death of an infant younger than 1 year of age, which remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and comprehensive review of the clinical history. The risk of SIDS in the United States is <1 per 1000 live births and the rate of SIDS peaks between 2 and 4 months of age. The incidence of SIDS had declined dramatically since the initiation of the "Back to Sleep" campaign, which encourages caregivers to place infants in a supine position for sleep.

Numerous risk factors for SIDS have been identified including maternal factors such as (1) young maternal age, (2) maternal smoking during pregnancy, and (3) late or no prenatal care. Infant or environmental factors include (1) preterm birth and/or low birth weight, (2) prone sleeping position, (3) sleeping on a soft surface and/or with bedding accessories such as loose blankets and pillow, (4) bed-sharing (sleeping in parents' bed), and (5) overheating.

More than 95 % of SIDS cases are associated with one or more risk factors, and in many cases, the risk factors are modifiable. The prone sleeping position is the strongest modifiable risk factor for SIDS. A theory that has been proposed in terms of etiology involves a triple-risk model. This suggests that SIDS occurs in infants at a vulnerable developmental stage of the central nervous system. These infants may have an underlying vulnerability, such as a brainstem abnormality and then experience a triggering event, such as airflow obstruction or being exposed to an environment with smoke. To minimize the risk for SIDS, parents should be educated on the risk factors, prenatally as well as at each well-infant visit. The use of home monitors has not been proven to reduce the incidence of SIDS and is not recommended [41,42].

Other Common Problems of the Infant

Table 5 provides short summaries of common problems of infancy and their management.

Family and Community Issues

Child Care

More than 50 % of infants under 1 year of age have parents who work outside the home. A quality child care setting supports normal infant development while protecting health and safety. Children in day care are 2–18 times more likely to contract certain infectious conditions including enteric, respiratory, and herpesvirus infections [43]. The optimal adult-to-child ratio for children under 1 year old in day care is 1:3. Staff should be trained in child development, be paid sufficiently to minimize turnover, and engage in recommended sanitation practices, such as washing their hands after diapering and before food preparation.

Risks and Resources

Normal infant development is promoted by fostering a family's strengths and resources while attempting to mitigate risk factors. Infant risk factors include: chronic illness, physical disability, lower birth weight, delayed growth, and developmental delay. Family risk factors include: physical abuse, family violence, neglect, parental depression, chemical dependence, and chronic illness. Environmental factors include poverty and toxins such as lead. Screening for risk factors should begin during prenatal care. Early intervention programs promote healthy development when families face these types of obstacles. Effective early intervention includes five elements:

1. Crisis intervention – addressing immediate threats to safety such as violence, abuse, or severe neglect.
2. Family-centered care – collaboration with parents to avoid labeling a child or parent. Challenges as well as strengths and resources should be identified.
3. Social support – assisting families to identify sources of support, such as family members, friends, and religious or community groups.
4. Community resources – linking families to existing programs that can help meet specific needs (e.g., specialized day care or parenting classes).
5. Ecologic model of intervention – assessing the individual infant, family, and physical environment to customize interventions that build on family strengths. Intervention should be culturally sensitive and nonstigmatizing.

Table 6 lists recommended screening questions to family risks and resources.

Partner Violence

One in five pregnant women experience intimate partner violence during their pregnancy, with higher rates among adolescent pregnant women [44] (see also chapter "▶ Domestic Violence"). Partner violence exerts well-documented negative impacts on maternal and infant health. Pregnant women who are experiencing abuse are more likely to delay seeking prenatal care and demonstrate higher rates of depression, anxiety, suicide attempts, alcohol and drug abuse, and smoking. Intentional injury, often the result of intimate partner violence, is one of the leading causes of death

Table 5 Approaches to common problems of the infant

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 q4–6h until clear X48 hours
Nasolacrimal duct obstruction (see Table 1). Symptoms usually delayed until days to weeks after birth. Rx: nasolacrimal massage tid 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 > several weeks or any deviation >4 months of age
Hearing loss. Screening recommending after delivery by American Academy of Pediatrics: 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 audio logic 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 and other systemic effects not caused by teething. Rx: chewing on soft cloth, teething ring, dry toast hastens eruption; topical and 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 and urinary tract infection. Risks (small): 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 thrush
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/VI 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: 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

(*continued*)

Table 5 (continued)

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 breast feeding. 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 (Citrocel); severe disease may require 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: position prone for neonates; elevate head of bed for older infants. Thickened feedings with cereal; acid suppression if esophagitis. If more severe, consider metoclopramide (side effects are common); surgery if medical therapy fails
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 formula 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) between ages 6 and 9 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)

among pregnant women. Current research demonstrates that infants born to abused women are more likely to experience preterm birth and be born at low birth weight. Family physicians can play a valuable role by screening all pregnant women for intimate partner violence at multiple points during prenatal care [44].

Infants of Substance-Abusing Mothers

Tobacco exposure during pregnancy is associated with miscarriage, placental abruption, late pregnancy bleeding and placental abruption, preeclampsia, and intrauterine growth restriction. Fetal alcohol syndrome includes the well-described triad of growth restriction, nervous system abnormalities, and midfacial hypoplasia, with possible involvement of cardiac and renal systems. The full syndrome involves heavy drinking throughout pregnancy, but lower levels of exposure also affect fetal development. Cocaine use during pregnancy is associated with preeclampsia, placental abruption, intrauterine growth restriction, and withdrawal symptoms in the neonate [43].

Exposure to one substance is often confounded by the abuse of other drugs and social and

Table 6 Assessing resources and risks for early family development

Concept	Interview questions
Social support	Do you have at least one friend or relative you can turn to for support and advice?
	Do you work, attend school, or participate in a religious community?
Housing	Do you have any concerns about housing?
Child care	Do you have any concerns about child care?
Transportation	Do you have any concerns about transportation?
Finances	Will you have any problems paying for food and clothing? Vitamins and medications? Health care?
Safety	During the past year, has anyone you know:
	Made you afraid for your safety?
	Pushed, kicked, slapped, hit, or otherwise hurt you?
	Forced sexual or physical contact?
	Tried to control your activities, your friends, or other parts of your life?
	Do you have any guns in your house?
	Do you have any concerns about safety or violence in your neighborhood?
	Do you use a seat belt when you ride in a car?
	Do you use an infant or car seat for each infant and toddler in your family?
	Do your children always use a seat belt?
Personal health	In general, how healthy do you consider yourself? (Excellent, good, fair, or poor)
STI and HIV risk	Have you ever had herpes, gonorrhea, chlamydia, trichomonas, genital warts, or a pelvic infection?
	Have you had two or more sexual partners in the past year?
Emotions	During the last 30 days, how much of the time have you felt downhearted and blue? (Very little, sometimes, often, most of the time)
Alcohol and drugs	Have your parents had any problems with alcohol or drugs?
	Does your partner have any problems with alcohol or drugs?
	Have you had any problems in the past with alcohol or drugs?
	During the past 30 days, on how many days did you have at least one drink of alcohol?
	During the past 30 days, on how many days did you have five or more drinks of alcohol in a row, that is, within a couple of hours?
Tobacco or electronic cigarettes	Does anyone in your home smoke tobacco or use electronic cigarettes?
	Do you currently smoke or use tobacco or electronic cigarettes?

environmental factors that correlate with chemical dependence and are known to affect infant outcome. Parents should be encouraged to seek treatment for substance abuse or chemical dependence at any point during pregnancy or after birth, as intervention at any point can improve outcomes.

Adolescent Parents

Adolescent women with access to appropriate pre- and postnatal resources can give birth to healthy children with normal developmental outcomes. Many adolescent pregnant women, however, experience other risk factors such as poverty, lack of access to health care, family violence, and substance abuse. When working with adolescent parents, the family physician should:

1. Expect a positive outcome while offering respect and dignity.
2. Encourage family support, if appropriate, including support of the father of birth and his family.
3. Encourage use of community resources such as child care, parenting classes, education, and early intervention programs.
4. Initiate family planning early during the pregnancy.
5. Encourage continued education and delay of the birth of another child.

Public Policy

Federal law PL99-457 encourages states to develop programs that identify and provide services to at-risk children from birth to 3 years of age. These early intervention programs are to be individualized, are family centered, and involve the primary health-care provider. Implementation varies from state to state, making it important for family physicians to familiarize themselves with local programs and resources.

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Family Medicine
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Infectious Diseases of Children

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Introduction

Infections are the most common cause of acute illness in children. Most commonly these are respiratory infections which peak when the child starts to go to school or out-of-home day care. Although the majority of these diseases have benign course, they cause significant discomfort, anxiety, missed work, and stress to many families caring for children. Frequent office visits, and unnecessarily prescribed medications, and sometimes dubious home remedies can be reduced by following best evidence-based practice and having a good doctor-patient (and parent) relationship.

In developed countries, morbidity and mortality from infections have declined dramatically, and deaths from infectious diseases are uncommon. However, serious infections still occur, e.g., meningococcal septicemia, meningitis, and multidrug-resistant pathogens, and some have reemerged, for example, tuberculosis and PVL-toxin-secreting *Staphylococcus aureus*, which requires early recognition and treatment. With an increase of global air travel, tropical diseases are encountered in all countries. In addition, epidemics may spread widely, e.g., SARS and H1N1 influenza, with children (and the elderly) being the most vulnerable.

Family physicians spend about 10 % of their time caring for children. About two-thirds of practicing family physicians report that they provide care for children [1]. Thus, the family physician's role in early proper management of infections is of paramount importance. Office visits must concentrate on clinical evaluation and diagnosis, appropriate management and advice, and prevention and early detection of complications. In this chapter, the clinical presentations, differential diagnosis, and management of common acute infectious diseases in children will be discussed.

Acute Upper Respiratory Tract Infections (URTIs)

The common cold or URTI is the third most common primary diagnosis in outpatient practice.

Patients seek care for URTIs throughout the year, especially in winter, with young children commonly experiencing five to eight colds a year [2, 3]. Day-care attendance is a major risk factor for URTI in young children. Other risk factors include smoking in the home, poor nutrition, and crowded living conditions [4–6]. Colds are most commonly caused by rhinovirus although other viruses have been isolated from children presenting with typical cold symptoms such as adenoviruses, coronaviruses, enteroviruses, influenza virus, parainfluenza virus, and respiratory syncytial virus (RSV) [7]. Direct inoculation has been the main mode of transmission; rhinoviruses are detectable on the hands of 40–90 % of cold sufferers; viruses also can be transmitted through coughing, sneezing, and nose blowing [8, 9].

Signs and symptoms of the common cold include some combination of nasal congestion and discharge, sore throat, cough, fever, hoarseness, mild fussiness or irritability, decrease in appetite, sleep disturbance, and mild eye redness or drainage. Although most of viral URTIs are self-limited, the family doctor must

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Table 1 Differential diagnosis of a child presenting with cold symptoms

Diagnosis	Signs and symptoms	Diagnostic test	Management
Viral URI	Some combination of the following: Nasal congestion and discharge, fever, sore throat, cough, hoarseness, mild fussiness or irritability, decrease in appetite, sleep disturbance, mild eye redness, or drainage [3]	Clinical picture Usually no testing is needed	Symptomatic treatment: Complementary therapy such as vapor rub, zinc sulfate syrup, buckwheat honey (avoid in children <1 year old – risk of botulism), nasal irrigation with saline, high-dose inhaled corticosteroids (for children who are wheezing) Prophylaxis: Complementary therapies such as probiotics, Vitamin C, Chizukit herbal preparation, nasal saline irrigation [8]
Acute bacterial rhinosinusitis (ABRS)	Any of the following presentations: Persistent illness [nasal discharge (of any quality) *or* daytime cough *or* both lasting more than 10 days without improvement] A worsening course (worsening or new onset of nasal discharge, daytime cough, or fever after initial improvement) Severe onset (concurrent fever/temperature ≥39 °C and purulent nasal discharge for at least 3 consecutive days) [10, 11]	NO routine imaging studies are needed CT or MRI for sinuses ONLY when a child is suspected of having orbital or central nervous system complications of ABRS [10, 11]	Antibiotic Rx for severe onset or worsening course (signs, symptoms, or both) Prescribe antibiotic therapy *or* offer additional outpatient observation for 3 days to children with persistent illness Amoxicillin with or without clavulanate is first-line treatment In penicillin-allergic patients, second of third-generation cephalosporins or levofloxacin or clindamycin plus a third-generation oral cephalosporin (cefixime or cefpodoxime) Reassess if there is either a caregiver report of worsening (progression of initial signs/symptoms or appearance of new signs/symptoms) or failure to improve within 72 h of initial management: *consider modification of antibiotic for the child initially managed with antibiotic if worsening symptoms or failure to improve **or* initiate antibiotic treatment for the child initially managed with observation [10, 11]
Group A streptococcal pharyngitis (GAS)	Sudden onset of sore throat in a child aged 5–15 years Systemic symptoms (fever, headache, occasional nausea, vomiting, abdominal pain) Tonsillopharyngeal erythema, patchy tonsillopharyngeal exudates, palatal petechiae	Throat swab for rapid antigen detection test (RADT) and/or culture Negative RADT should be backed by throat culture Not indicated for children <3 years old [12]	Antibiotic for 10 days (except azithromycin for 5 days) as follows: for non-penicillin-allergic patients, penicillin or amoxicillin (drugs of choice); *for penicillin-allergic individuals (not anaphylaxis), first-generation cephalosporin Clindamycin, clarithromycin, or

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Table 1 (continued)

Diagnosis	Signs and symptoms	Diagnostic test	Management
	Anterior cervical adenitis (tender nodes), scarlatiniform rash Winter and early spring presentation. History of exposure to strep pharyngitis [12]		azithromycin Adjunctive therapy to manage symptoms: acetaminophen or NSAIDS;*DO NOT use aspirin; *use of corticosteroids is NOT recommended [12]
Acute otitis media (AOM)	Moderate to severe bulging of the tympanic membrane (TM) *or* new onset of otorrhea not due to acute otitis externa *or* mild bulging of the TM *and* recent (less than 48 h) onset of ear pain or intense erythema of the TM [13]	AOM should not be diagnosed in children who do not have middle ear effusion (MEE) (based on pneumatic otoscopy and/or tympanometry) [13]	Analgesics if pain is present Antibiotics should be prescribed for all children less than 6 months old, children ≥6 months old with bilateral or unilateral AOM with severe signs or symptoms, and 6–23-month-old children with bilateral AOM without severe signs or symptoms Antibiotic therapy or observation offered with close follow-up for 6–23-month-old children with nonsevere unilateral AOM and ≥24-month-old children with nonsevere AOM (either unilateral or bilateral) [13]
Whooping cough (pertussis)	Coughing illness lasting 2 weeks with one classic sign of pertussis (paroxysmal cough, post-tussive emesis, or inspiratory whoop), without another apparent cause [14]	Culture and polymerase chain reaction (PCR) testing recommended by CDC [14]	Antibiotics: azithromycin, clarithromycin, or erythromycin base;*TMP/SMX for patients who cannot tolerate macrolides; clindamycin as third line Prophylaxis: same antibiotics in same doses for contacts of case within 21 days onset of symptoms in index case Prevention: vaccination [14]
Community-acquired pneumonia (CAP)	Fever, cough, dyspnea and tachypnea, pleuritic chest pain, abdominal pain, rhonchi [3, 15]	CXR, antigenic testing for RSV and influenza A and B [15]	Hospitalization vs outpatient treatment clinical decision Empiric antibiotic treatment for 7–10 days if the clinical diagnosis favors CAP: oral amoxicillin is the drug of choice for mild CAP; macrolides (azithromycin or clarithromycin) are good alternative for penicillin-allergic patients and are the drug of choice for children 6–18 years old Symptomatic treatment: analgesics antipyretics for fever and pain (acetaminophen or ibuprofen) [15]

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Table 1 (continued)

Diagnosis	Signs and symptoms	Diagnostic test	Management
Acute bronchitis/ bronchiolitis	For bronchitis: Cough (lasting more than 7–10 days up to 3 weeks in older children) and or wheezing; no fever; no nasal congestion or rhinorrhea; no respiratory distress For bronchiolitis: Cough, fever, rhinorrhea, wheezing, labored respirations, occasional hypoxia [16, 17]	For bronchitis: Clinical diagnosis; no tests are necessary For bronchiolitis: No laboratory or imaging needed for diagnosis; selected severe cases need admission to hospital with work-up as clinically appropriate [16, 17]	For bronchitis: No antibiotics as routine empiric treatment Symptomatic treatment: NO antitussives or expectorants, may use corticosteroid inhalers for wheezing Alternative therapies (*see treatment of cold symptoms in this table*) For bronchiolitis: Clinical decision: hospitalization according to risk factors and severity, fluid hydration, oxygen as needed, palivizumab only used according to strict guidelines, NO albuterol, NO epinephrine, NO systemic corticosteroids, NO antibiotic Rx unless there is evidence of concomitant bacterial infection [16–18]
Epiglottitis	Toxic appearance, alteration in voice, severe sore throat and dysphagia, stridor, drooling [3]	Clinical diagnosis Occasionally lateral neck X-ray and WBC count if clinical diagnosis is unclear [3, 17]	Needs immediate evaluation at appropriate site and ENT consultation [3]
Croup	Hoarseness, barking cough, low-grade fever, different degrees of respiratory distress (e.g.,, nasal flaring, respiratory retraction, inspiratory stridor) [3, 19]	Clinical diagnosis Only selected severe or atypical cases need work-up to rule out other causes [19]	General care: keep child calm, comfortable positioning; AVOID croup tent; oxygen if hypoxia; systemic corticosteroids (dexamethasone); nebulized epinephrine for severe cases [19]

recognize the signs of a serious illness early (respiratory distress, low level of responsiveness and activity, dehydration and vomiting, meningeal signs, and the presence of petechiae or purpuric rash) [3]. A diagnosis of viral URI also must be differentiated from a group of diagnoses that require specific management (Table 1 summarizes these diagnoses, their clinical presentation, diagnostic methods, and principles of their management).

The most important strategy in management of the common cold is education of patients, parents, and caregivers; they should be educated on prevention, comfort measures, and treatment recommendations. Handwashing or the use of hand sanitizers has been recommended as the best method to prevent the spread of viral upper respiratory infection; in addition encouraging breastfeeding and evaluation of day-care conditions for children have shown reduction in duration and severity of ARTIs. Comfort measures commonly used by parents, including some of complementary therapies listed in Table 1, are good choices that may help to control the symptoms and avoid the unnecessary use of antibiotics which are not indicated in the treatment of viral URTIs. Parents should be advised against the use of OTC cold and cough medicines for children younger than 6 years of age both because of the lack of benefit and also the potential harm that these preparations can result in. In addition parents should be educated about the

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office call-back instructions (If fever lasts 3 days or more, symptoms worsen after 3–5 days or if new symptoms appear, or if symptoms have not improved or resolved after 7–10 days) [3, 8].

Acute Bacterial Rhinosinusitis (ABRS)

Though most viral ARTIs involve the paranasal sinuses, only a small minority are complicated by bacterial sinusitis (6–8 %), and the majority of ABRS follow viral URTIs. Diagnosis of ABRS is made based on the clinical picture. The color of nasal discharge cannot be relied on to differentiate between a viral or bacterial etiology. ABRS is usually caused by *Haemophilus influenzae*, and *Moraxella catarrhalis*, or *Streptococcus pneumoniae*. Antibiotic use remains the mainstay of treatment in the latest Infectious Diseases Society of America (IDSA) guidelines. Neither antihistamines nor decongestants are recommended because they are unlikely to be of benefit and may have adverse effects [10, 20].

Group A Streptococcal Pharyngitis (GAS)

GAS is the most common bacterial cause of acute pharyngitis, responsible for 20–30 % of pharyngitis in children. Accurate diagnosis of streptococcal pharyngitis followed by appropriate antimicrobial therapy is important for the prevention of acute rheumatic fever and for the prevention of suppurative complications (e.g., peritonsillar abscess, cervical lymphadenitis, mastoiditis, and, possibly, other invasive infections). The signs and symptoms of GAS and nonstreptococcal pharyngitis overlap so broadly that accurate diagnosis on the basis of clinical grounds alone is unreliable. Therefore, it is advisable for family physicians to follow the ISDA clinical practice guidelines for proper diagnostic test use and antibiotic prescription for all children with GAS where possible (Table 1) . In addition to viral pharyngitis, other less common or rare causes of pharyngitis must also be considered when the tests for GAS are negative, or the clinical picture is suggestive. Infectious mononucleosis caused by Epstein-Barr virus and diphtheria caused by *Corynebacterium diphtheriae* are examples [12].

Acute Otitis Media (AOM)

AOM is usually a complication of eustachian tube dysfunction that occurs during a viral upper respiratory tract infection. *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* are the most common organisms isolated from middle ear fluid. Accurate diagnosis in the updated American Academy of Pediatrics (AAP) guideline endorses stringent otoscopic criteria for diagnosis. Otitis media with effusion (OME) is defined as middle ear effusion in the absence of acute symptoms. If OME is suspected and the presence of effusion on otoscopy is not evident, pneumatic otoscopy, tympanometry, or both should be used to make the diagnosis. AAP guidelines recommend against antibiotic use in OME and also provide detailed guidelines of appropriate antibiotic use in children diagnosed with AOM [13, 21].

Respiratory Syncytial Virus Infections (RSV)

Respiratory syncytial virus (RSV) causes respiratory tract infections in children. Lower respiratory tract infections (e.g., bronchiolitis, pneumonia) are more common in children younger than 2 years, whereas upper respiratory tract infections tend to affect older children. Since previous infection does not protect children against reinfection, it is common for the family doctor to see patients with repeated RSV infections. Adherence to the American Academy of Pediatrics clinical practice guidelines for the diagnosis and management of bronchiolitis can decrease unnecessary diagnostic testing and intervention. In most previously healthy children, an RSV infection is self-limited and responds to supportive care. Children with unrepaired cardiac disease or chronic lung disease are at increased risk of severe RSV infection. Premature children and the very young (less than 3 months old) tend to be more at risk of having severe symptoms and therefore may require hospitalization.

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Table 2 Differential diagnosis of viral exanthems in children

Viral exanthem	Etiology/ infectivity	Clinical manifestations/ incubation period (IP)	Diagnostic methods	Treatment	Prevention	Complications
I macular and maculopapular exanthems						
Measles (rubeola) [22, 23]	RNA measles virus/highly contagious	IP:10–12 days Prodrome: fever, coryza, conjunctivitis, rhinorrhea, sore throat, and a dry cough Enanthem: Koplik' s spots Exanthem: 3–4 days later, begins behind the ears and hairline area, spreads over the rest of the skin over few days, resolves in the same order as its appearance, and will often desquamate	Clinical presentation Serum measles IGM test for confirmation	No specific antiviral therapy for measles Treatment of symptoms	Measles vaccine alone or as part of MMR vaccine	Transient immune suppression Acute postinfectious encephalitis Subacute sclerosing panencephalitis (SSPE)
Rubella (German measles) [22, 24]	RNA rubella virus/highly contagious	IP: 3–4 weeks Prodromal symptoms, which include low-grade fever, headache, sore throat, and myalgias Exanthema stage: appears after 2–5 days and spreads in a cephalocaudal pattern Symmetrical lymphadenopathy in postauricular and occipital areas, arthralgias, and arthritis	Serum rubella IGM titer test	No specific antiviral therapy for rubella Supportive treatment	Rubella vaccine alone or part of MMR vaccine	Congenital rubella syndrome (deafness, cataracts, and cardiac disease)
Erythema infectiosum (fifth disease) [22]	DNA Parvovirus B19	IP: 1–2 weeks First stage: fiery-red facial erythema (slapped cheeks) Second stage: 3–4 days later (rash over proximal extremities) Third stage: exanthem recurs intermittently in response to stimuli (local irritation, high temperatures, and emotional stress)	Clinical Diagnosis ELISA test highly sensitive; however, false positive results may recur PCR test is available	Supportive At-risk patients may require transfusions or intravenous immunoglobulin therapy	No specific preventive measure Handwashing might be helpful during epidemics	Transient aplastic crisis, chronic red cell aplasia, hydrops fetalis, or congenital anemia

		Asymmetric large joint arthropathy (10 % of patients)				
Roseola infantum	Human herpesvirus (HHV) types 6 and 7	IP:5–15 days High fever (3–5 days),followed by the acute onset of a rosy pink, nonpruritic macular rash, predominantly on the neck and trunk; leukopenia	Clinical diagnosis No available standardized lab test	Supportive treatment	No specific preventive measures	Febrile seizures
II vesicular and pustular exanthems						
Varicella (chickenpox) [22, 25]	DNA varicella zoster virus (VZV) Highly contagious during IP and active skin rash	IP: 2–3 weeks Two different clinical presentations: Varicella manifestations: Prodromal stage: fever, malaise, and myalgias Exanthem stage: begins in the hairline and spreads in a cephalocaudal pattern, involving the scalp and mucous membranes, vesicle crust (within 4–5 days of onset of the initial lesion), older lesion crust over as newer lesions form (polymorphous exanthema); lesions may heal with hypopigmentation and scarring Herpes zoster (shingles) manifestation: unilateral vesicular skin eruption involving one to three dermatomes, may be painful or pruritic Usually a benign, mild, self-limiting disease (in immunocompetent individuals)	Clinical Diagnosis Can be confirmed by skin scraping testing for the antigen with immunofluorescence	Oral acyclovir (ACV) is not routinely recommended except for adolescents (for 5 days, starting within 24 h of rash development) Symptomatic treatment for fever (only use acetaminophen) and pruritus (calamine lotion and colloidal oatmeal baths)	Varicella vaccine	Immunocompetent children: bacterial superinfection, due to group A *Streptococcus* or *Staphylococcus aureus* Immunocompromised patients are at risk for severe and protracted varicella, multiorgan involvement, and hemorrhagic varicella
Hand, foot, and mouth disease	Coxsackie A16 virus, other Coxsackie,	IP: 3–7 days Prodrome: fever, lymphadenopathy Exanthem: 1–2 days later	Is a clinical diagnosis Can be confirmed by	No specific treatment Symptomatic	No specific measures Handwashing, surface	Rare: neurological or cardiopulmonary complication

(*continued*)

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Table 2 (continued)

Viral exanthem	Etiology/ infectivity	Clinical manifestations/ incubation period (IP)	Diagnostic methods	Treatment	Prevention	Complications
(HFMD) [22]	and enteroviruses	painful vesicles on the palmar and plantar skin, buccal mucosa, and tongue Resolves in 5–7 days	isolating the virus from vesicles		cleaning, and disinfection	(meningoencephalitis or myocarditis)
III Papular exanthem, e.g., papular acrodermatitis of childhood (PAC) [22]						
IV Other viral exanthems, e.g., pityriasis rosea, erythema multiforme, nonspecific viral exanthems [22]						

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Supportive treatment, including hydration, good airway management, and oxygenation, is the mainstay of RSV management [17, 18].

Croup/Epiglottitis

Croup is a syndrome that includes spasmodic croup (recurrent croup), laryngotracheitis (viral croup), laryngotracheobronchitis, and laryngotracheobronchopneumonitis, with recurrent and viral croup being the most commonly encountered. The incidence of croup often peaks during the fall season, although sporadic cases may occur throughout the year. Croup is usually caused by viruses, with parainfluenza virus (type 1) being the most common. Other viruses that cause croup are enterovirus, human bocavirus, influenza A and B viruses, respiratory syncytial virus, rhinovirus, and adenovirus.

Both recurrent croup and viral croup have the same clinical presentation, with the exception that recurrent croup tends to recur and typically lacks associated symptoms of respiratory tract infection. Although croup tends to have a benign course, a differential diagnosis of more serious but less common conditions must be entertained. Bacterial tracheitis may result from a secondary infection, most often due to *Staphylococcus aureus* or *Streptococcus pneumoniae*, and usually leads to a more toxic appearance, with higher fever and severe respiratory symptoms. Bacterial tracheitis does not respond to usual croup treatment. Intravenous antibiotics are needed, and intubation may become necessary. Epiglottitis (supraglottitis) is a life-threatening bacterial infection of the upper airway almost always caused by *Haemophilus influenzae* type b (Hib). The incidence has declined dramatically as a result of the use of Hib vaccine. Other diagnoses to consider include foreign body aspiration, peritonsillar abscess, retropharyngeal abscess, and angioedema [19]. Principles of management of croup and epiglottitis are summarized in Table 1.

Viral Exanthems

An exanthem is a widespread erythematous rash that is accompanied by systemic symptoms such as fever, headache, and malaise. In children, exanthems are usually associated with infections, and viral infections are the most common. Determining the cause of an exanthem is based on the characteristic morphology, distribution and time course of the eruption, and a careful assessment of infectious contacts, immunization status, and aspects of the physical examination. Table 2 shows the common skin rash morphologies associated with viral infections, their causative agents, clinical presentation, diagnostic tests needed, treatment and prevention methods, and complications. Although uncommon, serious acute illnesses with skin rash must be identified immediately; for example, a skin rash in a child with meningeal signs is an indicator of life-threatening condition (meningococcemia) that warrants immediate hospital referral and treatment. Kawasaki disease also is a childhood illness with rash that must be diagnosed and treated early to ensure better prognosis. The classic viral exanthems have been discussed; other important skin rashes related to viral infections and bacterial infections (e.g., scarlet fever), in addition to other noninfectious causes such as drug eruptions, must be considered in the differential diagnosis. New viral-associated exanthems have been identified; papular acrodermatitis of childhood (PAC) is now recognized to be a manifestation of a number of infectious agents, including viruses. The ability to detect parvovirus B19 virus in seronegative patients using PCR has been useful in linking the virus to erythema infectiosum, as well as other viral exanthems. The viral role in another group of exanthematous disease is yet to be fully identified (e.g., Kawasaki disease, pityriasis rosea, and erythema multiforme) [22, 26].

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Kawasaki Disease (KD)

KD is an acute vasculitis of childhood that predominantly affects the coronary arteries. An infectious etiology is suspected based on epidemiological and clinical data; however as of today, the cause of KD remains unknown. In the United States, KD is more common during the winter and early spring months, in boys more than girls, in children younger than 5 years old, and in children of Asian ethnicity [27]. The classic clinical presentation of KD includes at least 5 days of fever plus four or more of the five major clinical features (conjunctival injection, erythema of the lips and oral mucosa, polymorphous skin rash, cervical lymphadenopathy (with one of the nodes being at least 1.5 cm in diameter),and swelling or redness of the extremities). The classic peeling of the fingers and toes (starting in the periungual region) usually does not occur until 2–3 weeks after onset of symptoms. In addition, classic KD can be diagnosed with three of the above clinical features if coronary artery abnormalities are observed on echocardiography. "Incomplete KD" refers to patients who do not fulfill the classic criteria and is more common in children younger than 1 year. In this group, the rate of coronary artery aneurysms is paradoxically higher if not treated. Some children with KD develop coronary artery aneurysms or ectasia, ischemic heart disease, and sudden death. Therefore early clinical suspicion and diagnosis are important [28]. Nonspecific lab tests such as the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) may suggest the diagnosis of Kawasaki disease because they are often unusually highly elevated. In patients with compatible features, and elevated CRP levels or ESR, supplemental laboratory test results are often seen (these include leukocytosis with shift to the left, mild anemia, thrombocytosis, proteinuria and sterile pyuria on urine analysis, hypoalbuminemia, and elevated serum transaminases). Cardiac manifestations for any suspected case of KD might be detected earlier by performing echocardiography. Initial treatment with a single dose (2 g per kg) of intravenous immunoglobulins (IVIG) and high-dose aspirin (80–100 mg per kg per day, divided into four doses) is recommended. Treatment is preferably started as soon as possible, optimally within the first 10 days of fever; however, treatment is still recommended if patients present after 10 days and still have fever and manifestations of inflammation. Low-dose aspirin (3–5 mg per kg per day, given as a single dose) has an antiplatelet effect and should be continued for 6–8 weeks after disease onset if there are no coronary artery abnormalities or indefinitely if abnormalities are present. Children on long-term aspirin therapy should receive an annual influenza vaccination. Also, parents should be told to contact their physician if symptoms of influenza or varicella arise, because alternative agents to aspirin might be considered. Children who have Kawasaki disease without evidence of abnormalities on echocardiography appear to return to their usual state of health without any cardiac sequelae. The current American Heart Association guidelines provide a stratification system to categorize patients by their risk of myocardial infarction and provide guidelines for management [27, 28].

Gastrointestinal Infections

Acute Gastroenteritis

Although often considered a benign disease, acute gastroenteritis remains one of the major causes of morbidity and mortality in children around the world, accounting for 10.5 % of deaths among children younger than 5 years of age [29].

Etiology

By far, viruses remain the most common cause of acute gastroenteritis in children, both in the developed and developing world. Rotavirus represents the most important viral pathogen worldwide; it is responsible for 20–60 deaths per year in the United States and up to 500,000 deaths from diarrhea worldwide [30].

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Viral infections, primarily from rotavirus, cause 75–90 % of infectious diarrhea cases in the industrialized world. Bacterial pathogens cause another 10–20 % of cases, with as many as 10 % of these occurring secondary to enterotoxigenic *Escherichia coli* (e.g., traveler's diarrhea). Parasites such as *Giardia intestinalis* and *Cryptosporidium* cause fewer than 5 % of cases [31]. In the United States, routine rotavirus vaccination has led to a 60–75 % reduction in pediatric rotavirus hospitalization since 2006. With the continued decline of rotavirus-associated gastroenteritis, noroviruses (Norwalk-like viruses) have become the leading cause of medically attended acute gastroenteritis in children younger than 5 years in that country [32].

Clinical Picture

The clinical presentation is the mainstay of diagnosis, and therefore careful history and physical examination will serve to differentiate gastroenteritis from other causes of vomiting and diarrhea in children. These will also help in estimating the degree of dehydration. Diarrhea is the main presenting symptom and is usually defined as three or more watery or loose stools in 24 h. The duration of diarrhea, the frequency and amount of stool, the time since the last episode of diarrhea, and the quality of stools must also be determined. Frequent, watery stools are more consistent with viral gastroenteritis, while stools with blood or mucous are indicative of a likely bacterial pathogen. Similarly, a long duration of diarrhea (>14 days) is more consistent with a parasitic or noninfectious cause of diarrhea. Vomiting is another important symptom, the duration of vomiting, the amount and quality of vomitus (e.g., food contents, blood, bile), and the time since the last episode of vomiting must be determined. Signs of systemic infection must be noted (fever, chills, myalgias, rash, rhinorrhea, sore throat, cough). Abdominal pain is another important symptom that the child or parent can report; in general, pain that precedes vomiting and diarrhea is more likely to be due to an abdominal pathology other than gastroenteritis. Urinary symptoms including frequency (measured by the number of wet diapers), time since last urination, color and concentration of urine, and presence of dysuria should be sought. Some important points in the general appearance and behavior are important to determine the degree of dehydration and subsequent management (weight loss, level of thirst, level of alertness, increased malaise, lethargy or irritability, quality of crying, and presence or absence of tears with crying). Travel history and recent antibiotic use are other important points in the history that may suggest the possibility of traveler's diarrhea or *C. difficile* infection [31, 33].

Management

Signs and symptoms of dehydration are important to determine the severity of dehydration. Both the Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics (AAP) recommend using a simple dehydration scale to classify the total body water loss occurring with dehydration as minimal/none (<3 %), mild/moderate (3–9 %), or severe (>10 %). Abnormal capillary refill (>2 s), decreased skin turgor, and abnormal respiratory pattern (hyperpnea) have been the most reliable signs of determining the severity of dehydration. The vast majority of children presenting with acute gastroenteritis do not require serum or urine tests, as they are unlikely to be helpful in determining the degree of dehydration. Laboratory values may be helpful in evaluating severe dehydration, for which intravenous fluids and electrolyte supplementation (especially potassium, bicarbonate, and sodium) are needed [31, 34]. Prevention of dehydration is the cornerstone of gastroenteritis treatment in children. A child with minimal or no dehydration should be encouraged to continue his or her usual diet plus drink adequate fluids. Early oral rehydration therapy using an oral rehydration solution (ORS), before the child becomes more severely dehydrated, is important and can be done at home.[5] The best way to accomplish early treatment is to train the physician's office staff to explain how to use an ORS when caregivers call for help at the beginning of a child's illness. Clear liquids, such as water, sodas, chicken broth, and apple

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juice, should not replace an ORS because they are hyperosmolar and do not adequately replace potassium, bicarbonate, and sodium. These fluids, especially water and apple juice, can cause hyponatremia. An ORS is composed of sodium, dextrose, and bicarbonate in a ratio that does not overwhelm the hyperactive bowel with a hyperosmolar solution, but that replaces the electrolyte loss. In general, antidiarrheal medications should not be used in children with acute gastroenteritis because they delay the elimination of infectious agents from the gastrointestinal tract

Prevention

Handwashing has been shown to reduce the incidence of gastrointestinal illness. Rotavirus vaccine is recommended as a routine immunization at 2, 4, and 6 months of age [35].

Pinworm Infestation (Enterobiasis)

Pinworm infection is caused by a small, thin, white roundworm called *Enterobius vermicularis*. Although pinworm infection can affect anyone, it most commonly occurs among children, institutionalized persons, and household members of persons with pinworm infection. Pinworm is the most common worm infection in the United States. Humans are the only species that can transfer this parasite. Pinworm eggs can survive in the indoor environment for 2–3 weeks. People who are infected with pinworm can transfer the parasite to others for as long as there is a female pinworm depositing eggs on the perianal skin. A person can also re-infect themselves [36, 37].

Clinical Presentation

A person infected with pinworm is often asymptomatic. However, perianal itching is the most common presentation. When the infection is heavy, it can present as a secondary bacterial infection in the perianal area due to the irritation and scratching. Often the patient will complain of bruxism and insomnia due to disturbed sleep. Infection of the female genital tract has been reported [36, 37].

Diagnosis and Treatment

Because of the life cycle of the pinworm, eggs and worms are often scarce in the stool; therefore, examining stool samples is not recommended. Identifying pinworm can be done by finding the female worm, which is about 10 mm long, in the perianal region 1 or 2 h after a child goes to bed at night, or by using a low-power microscope to identify ova on cellophane tape. The ova are obtained in the early morning before the child arises by patting the perianal skinfolds with a strip of cellophane tape, which is then placed sticky side down on a glass slide and viewed microscopically. This procedure should be repeated on five successive mornings; if necessary, eggs may also be identified by examining scrapings from underneath the patient's nails.

Any one of three antiparasitic medications (mebendazole, pyrantel pamoate, and albendazole) can be used for treatment. A single dose of any of these medications is given followed by another single dose 2 weeks later. The medications do not reliably kill pinworm eggs. Therefore, the second dose is to prevent re-infection by adult worms that hatch from any eggs that are not killed by the first treatment. Repeated infections should be treated by the same method as the first infection. In households where more than one member is infected or where repeated, symptomatic infections occur; it is recommended that all household members be treated at the same time. In institutions, mass and simultaneous treatment, repeated in 2 weeks, can be effective. Handwashing after using the toilet, changing diapers, and before handling food is the most successful way to prevent pinworm infection. In order to help prevent the spread of pinworm and possible re-infection, people who are infected should bathe every morning to help remove many of the

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eggs on the skin. Showering is a better method than taking a bath, because showering avoids potentially contaminating the bath water with pinworm eggs. Infected people should not co-bathe with others. Infected patients also must cut their fingernails regularly and avoid biting the nails and scratching around the anus. Frequent changing of underclothes and bed linens first thing in the morning is a great way to prevent possible transmission of eggs in the environment and risk of reinfection. These items should not be shaken and carefully placed into a washer and laundered in hot water followed by a hot dryer to kill any eggs that may be present [36, 37].

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Behavioral Problems of Children

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Attention Deficit/Hyperactivity Disorder

Attention deficit/hyperactivity disorder (ADHD) is a disorder of poor attention and/or impulse control that typically present in early childhood and has significant impact upon child functioning across environments. It is comprised of three different subtypes, ADHD-Predominately Inattentive, ADHD-Predominately Hyperactive/Impulsive, and ADHD-Combined, based upon presentation of symptomology.

ADHD: Predominately Inattentive

ADHD-Predominantly Inattentive is comprised of nine criteria, and six or more criteria must be present for at least 6 months. These symptoms must differ from normal developmental patterns and have a significant impact upon daily functioning. For children 17 years and older, only five of the nine criteria must be met for diagnosis [1].

Criteria include:

1. Poor attention to details and/or makes careless errors
2. Difficulty maintaining attention in daily activities, mind wanders
3. Appears distracted, does not appear to listen
4. Difficulty following/completing instructions, starts but does not complete tasks
5. Difficulty with organization, difficulty with sequential tasks, does not meet deadlines
6. Avoids activities that require sustained effort/focus
7. Frequently loses important items (homework assignments, books, extracurricular items)
8. Easily distracted by external activities
9. Forgetful in day-to-day activities, poor memory for obligations [1]

ADHD: Predominately Hyperactive/Impulsive

ADHD-Predominantly Hyperactive/Impulsive is comprised of nine criteria, and six or more criteria must be present for at least 6 months. These symptoms must differ from normal developmental patterns and have a significant impact upon daily functioning. For children 17 years and older, only five of the nine criteria must be met for diagnosis [1].

Criteria include:

1. Fidgety, difficulty sitting still, fine-motor hyperactivity in fingers/hands/legs
2. Leaves seat when expected to remain seated (classroom, dinner table)
3. Runs around and/or climbs on items (furniture, people), older children are restless
4. Excessively loud during activities, inability to play quietly
5. Moves frequently, unable to remain still, restless, appears to have excessive energy
6. Excessively talkative, does not share "talk-time"
7. Answers questions before they are completed, speaks out of turn, interrupts others
8. Difficulty waiting for their turn in activities
9. Interrupts others activities (disrupts others conversations or activities, uses other peoples things without permission, takes over/leads others activities without permission) [1]

ADHD: Combined Presentation

ADHD-Combined Presentation is comprised of 18 criteria, and 12 or more criteria must be present for at least 6 months. These symptoms must differ from normal developmental patterns and have a significant impact upon daily functioning. For children 17 years and older, only ten of the 18 criteria must be met for diagnosis [1].

To meet criteria for the disorder, symptoms must be present prior to 12 years of age, and impairments must be present in at least two environments (home, school, community, and/or employment for older teens) although symptom severity may vary across environments. Prevalence rates of ADHD in children range from 5 % to 8.5 %, and a portion of children with the disorder report symptoms into adulthood [1]. Symptoms of hyperactivity/impulsivity typically

present during the toddler years, while symptoms of inattention are identified once the child enters school, and symptoms impede academic performance [1–3]. Symptoms of hyperactivity tend to decrease with age, while symptoms of impulsivity and inattention remain constant. ADHD is twice as common in males compared to females, and males have higher rates of hyperactivity/impulsivity, while females have higher rates of inattention [1]. Rates of ADHD are higher in children with first-degree relatives who also have an ADHD diagnosis. Children with ADHD are at an increased risk for cognitive (lower academic attainment), behavioral (increased impulsive behaviors, incarceration), emotional (difficult interpersonal relationships), and psychological (conduct disorder, personality disorders, substance use) impairment compared to peers without ADHD [1–3].

ADHD: Cognitive-Behavioral Treatments

There are multiple cognitive-behavioral treatment (CBT) strategies to manage the symptoms of ADHD. It is preferred that CBT strategies be implemented prior to medication management and should be noted that CBT strategies may require a substantial time investment prior to observing symptom reduction. For symptoms that are severe and significantly influence the child across environments, it may be appropriate to implement both CBT strategies and medication management simultaneously and then decrease medication management as CBT methods become more consistently implemented and effective. Children with ADHD should be provided with tasks in small, manageable segments to increase the likelihood of success. Parents should provide verbal directions in developmentally appropriate language, and the child should repeat the directions to assure comprehension. Directions should be provided one at a time, and parents may advance to multi-step commands once symptoms are more manageable [2, 3]. Behavioral charts and token economies are affordable and efficient methods to monitor and manage ADHD symptoms. Behavioral charts should be developed for both home and school environments and elsewhere as appropriate. Children should be involved in determining problematic behaviors to decrease, desirable behaviors to increase, and consequences (positive and negative) for these behaviors. When children are involved in this process, they are more likely to be invested in behavioral change and to be motivated by the consequences [2, 3].

ADHD: Medication Management

Stimulant medications are typically prescribed for children with ADHD as these medications are affordable and fast acting with an immediate decrease in symptoms. The general rule with stimulant medications, especially in children, is to begin with the lowest possible dose and monitor for both improvements in symptomology and the presence of negative side effects (changes in sleep, appetite, irritability, etc.). If the child tolerates the medication with minimal and manageable side effects, then the dose may be increased in small intervals until a therapeutic level is obtained. Extended release (XR) medications are preferable to immediate release (IR) medications for several reasons. First, XR medications are taken once daily, typically with the morning meal at home prior to the beginning of the school day, and this limits social embarrassment for the child who must leave the classroom midday for a second dose of IR medications. Secondly, XR medication effects do not dissipate midday, compared to IR medications, at which time symptoms resume and may cause impairment. Thirdly, XR medications have lower abuse potential, and this should be considered when prescribing to children or adolescents at risk for medication abuse or diversion. Parental abuse or diversion of child IR medications is also a concern and should be considered. For children with severe ADHD symptoms, an evening IR medication may manage symptoms during homework assignments or afterschool activities. These medications should initially be started on a weekend compared to a school day to allow parents to monitor ADHD

symptoms and side effects and acclimate the child to the medication prior to use within the school environment. Psychosocial education should be provided regarding taking ADHD medications at the appropriate time due to impact upon sleep. Families should be encouraged to adhere to medication holidays on the weekends, school holidays, and summer breaks if possible. If medication holidays are observed, then prescriptions should be written for a 20–24-day supply instead of the standard 30-day supply. Parents should be educated regarding the potential for abuse or diversion, and medications should be kept in a safe location and monitored.

There are two approved stimulant medications for children 3 years of age and older (Adderall and Dexedrine) and multiple stimulants medications for children 6 years of age and older (Adderall, Concerta, Daytrana, Desoxyn, Dexedrine, Focalin, Intuniv, Metadate, Methylin, Ritalin, Strattera, and Vyvanse) [4]. Medication use prior to 3 years of age is discouraged due to developmental concerns.

Learning Disabilities

Learning disorders (LD) primarily affect cognitive functioning, although behavioral and emotional functioning are also impacted. There are three types of learning disorders, impairment in reading, written expression, and/or mathematics, based upon symptomology. Learning disorders are comprised of six criteria and one or more symptoms must be present for at least 6 months. Symptoms must differ from normal developmental patterns and have a significant impact upon daily functioning despite intervention [1].

Criteria include:

1. Imprecise, protracted, labored reading
2. Difficulty comprehending the significance of what has been read
3. Difficulties with spelling
4. Difficulties with written expression/writing structure
5. Difficulties understanding mathematic concepts
6. Difficulties understanding mathematical theory [1]

Symptoms of LD fall on a continuum from normal developmental difficulties when learning new material to abnormal behaviors that exceed expected difficulties when learning new material. Children must perform beneath academic expectations as corroborated by standardized intellectual and/or achievement assessments. Prevalence rates across all three types of learning disorders range from 5 % to 15 % in school-aged children [1]. Symptoms typically present during early school-age years when fundamental academic skills are being taught. However, the extent of symptomology may not become prominent until later academic years when exceedingly difficult educational endeavors are impacted by limited academic skills [1]. Symptoms are chronic without substantial academic intervention. Learning disorders are two to three times more common in males compared to females [1]. Rates of LDs are higher in children with first-degree relatives who also have LDs. Environmentally, children's academic attainment mirrors parental academic attainment. Children with LD are at an increased risk for cognitive (lower grades, less likely to graduate), behavioral (disruptive behavior trying to avoid cognitively demanding tasks), emotional (frustration, tearful), vocational (under-employed, unemployed, lower salary), and psychological (anxiety) impairment compared to peers without LDs [1, 5].

Learning Disorders: Cognitive-Behavioral-Emotional Treatments

Prior to implementing cognitive-behavioral treatments (CBT), it is crucial that the child completes intellectual and achievement standardized assessment to ascertain the specific types of learning difficulties as this will direct treatment planning. Based upon assessment results, providers will likely be requested to complete paperwork (504 Plans, Individual Educational Plans, and/or Student Assistant Team Plans) for academic accommodations. Tutors for educational needs

and a child psychologist/psychiatrist may be helpful in providing support for the child/family as they manage these disorders. Parental psychosocial education is invaluable to decrease parental anxiety/worry regarding the diagnosis and provide methods parents may employ to support their child as they manage symptomology. Cognitive components focus upon managing children's negative self-cognitions and altering teaching methods to be more effective for the child. Behavioral components include distributing assignments into more management segments, providing clear directions for assignments, assisting the child with mastering academic concepts, providing extra time to complete assignments and advance knowledge of major assignments, and implementing consequences (positive and negative) for effort and successes [5]. Emotional regulation components include teaching methods to self-soothe when frustrated or anxious such as progressive muscle relaxation and controlled breathing techniques.

Learning Disorders: Medication Management

At present, there are no medications that reduce the symptoms of learning disorders. However, medications may decrease symptoms of comorbid disorders, such as attention deficit/hyperactivity disorder or anxiety disorder, which may impede the learning process.

Temper Tantrums

Temper tantrums frequently occur during childhood and typically consist of verbal, physical, and emotional components. There are no specific or minimal criteria for this disruptive behavior. Components of temper tantrums will vary by developmental and chronological age and may evolve over time.

Components include:

1. Verbal: screaming/shouting, yelling, arguing, crying, whining, fussing
2. Physical: throwing self on floor, kicking, stomping feet, hitting self or others, hitting or throwing objects, biting self or others, breaking items, running away, pushing/pulling, pouting or other facial expressions
3. Emotional: anger, sadness, frustration, fear [6–10]

The age of onset, duration, frequency, and severity of temper tantrums should be considered when rendering a diagnosis. The majority of children engage in temper tantrums with age of onset occurring most frequently between 2 and 4 years of age, but temper tantrums may continue into adolescence [7, 8]. Prevalence rates of temper tantrums decrease with age as children more effectively manage their verbal, physical, and emotional responses to events [11]. Temper tantrums persisting past 5 years of age, lasting longer than 15 min, consisting of severe behaviors, and occurring in excessive of five times daily are likely indicative of abnormal development [7]. Temper tantrums are either reactive (responding to an event) or proactive (initiating an event) [12] and function to express an emotional response to an event, seek parental attention, avoid completing an undesired task, or to obtain a desired item [7]. Due to children's limited coping strategies, these emotional responses manifest as inappropriate verbal or physical behaviors [7, 8].

Temper Tantrums: Cognitive-Behavioral-Emotional and Medication Treatments

The treatments for temper tantrums, oppositional defiant disorder, and conduct disorder are similar and are located under conduct disorder.

Oppositional Defiant Disorder

Oppositional defiant disorder (ODD) is a pattern of angry or irate mood, argumentative and/or defiant behaviors, and/or spitefulness. There are eight

criteria, and four or more criteria must be present for at least 6 months and have a significant impact upon daily functioning. For children 4 years and younger, symptoms must be present on most days per week. For children 5 years and older, symptoms must be present at least once weekly [1].

Criteria include:

Anger/irate mood
1. Frequently loses temper
2. Easily aggravated
3. Angry and bears grudges

Argumentative/Defiant
4. Argues with others (peers, adults, authority figures)
5. Intentionally refuses to comply with reasonable requests from authority figures
6. Intentionally engages in annoying behaviors
7. Blames others for their misconduct

Vindictiveness
8. Spiteful or revengeful toward others at least twice in the last 6 months [1]

Symptoms of ODD fall on a continuum from normal developmental behaviors (conflict with siblings/peers and parents/authority figures) to abnormal behaviors (chronic, frequent, severe behaviors) that cause significant impairment. Prevalence rates of ODD range from 1 % to 11 % with an average of approximately 3 % in children [1]. ODD is 1.4 times more common in males compared to females, but equal rates are reported between genders in adolescence [1]. Rates of ODD are higher in children from household environments with harsh, unpredictable/unstable, and/or neglectful parenting practices. Rates of ODD are also higher in children raised in fragmented environments (foster care, kinship care, etc.) or multiple households (divorced parents). Children with ODD are at increased risk for difficulties across environments including home (family members, romantic partners), employment (supervisors, work colleagues), and community (coaches, religious persons) impairment compared to peers without ODD [1].

Temper Tantrums: Cognitive-Behavioral-Emotional and Medication Treatments

The treatments for temper tantrums, oppositional defiant disorder, and conduct disorder are similar and are located under conduct disorder.

Conduct Disorder

Conduct disorder (CD) is a chronic and continual pattern of behaviors in which social norms are violated and the basic rights of others are disregarded. There are 15 criteria and three or more criteria must be present for the last 12 months with at least one criteria present in the last 6 months. There are three disorder subtypes based upon age of onset including childhood onset (at least one symptom prior to 10 years of age), adolescent onset (no symptoms present until 10 years of age), and unspecified onset (unable to determine age of onset) [1].

Criteria include:

Aggression toward people/animals
1. Frequently engages in bullying, threatening, or intimidation practices
2. Instigates physical altercations
3. Used an instrument (weapon) that could cause life-threatening injury
4. Physically aggressive toward people
5. Physically aggressive toward animals
6. Stolen property while engaged in confrontation with an individual (mugging, etc.)
7. Forced others into sexual activities

Destruction of property
8. Engaged in arson with the intent of causing personal or property damage
9. Intentionally destroyed other's property (other means than arson)

Deceitfulness or theft
10. Illegally entered someone's home, building, or automobile
11. Uses deceit to attain items/favors or to avoid punishment/obligations
12. Stolen property while not engaged in confrontation with an individual (shoplifting, etc.)

Serious violations of rules

13. Breaks parental curfews prior to 13 years of age
14. Ran away from home at least twice or once staying away for an extended period of time
15. School truancy prior to 13 years of age [1]

Prevalence rates of CD in children are difficult to determine. Approximately 3–7 % of children and adolescents demonstrate verbal/physical aggressive behaviors, but these behaviors may not be sufficient to warrant a CD diagnosis [12]. Symptoms often present in early childhood but become problematic in middle childhood and adolescence, and symptom onset after 16 years of age is uncommon [1]. Individuals with this disorder typically first had a diagnosis of ODD. Rates of CD are higher in males compared to females [1]. Rates of CD are higher in children with first-degree relatives who also have a CD diagnosis. Environmentally, rates of CD are higher in children from household environments with harsh, unpredictable/unstable, neglectful parenting practices, excessive discipline, abuse, frequently changing caregivers, and a history of parental criminal behavior [1]. Community factors influencing CD symptoms include peer rejection, membership in delinquent peer groups, and high rates of community violence. Children with severe CD symptoms are at an increased risk for cognitive (negatively interprets events, overly suspicious of others), behavioral (verbal/physical altercations, poor self-regulation), emotional (poor emotion regulation, easily frustrated, irritable), psychological (substance abuse), and legal-social (extensive legal issues, incarceration, engagement in high-risk activities) impairment compared to peers without CD [1].

Temper Tantrums, ODD, and CD: Cognitive-Behavioral-Emotional Treatments

There are multiple cognitive-behavioral treatments (CBT) and emotional regulation strategies to manage symptoms of temper tantrums, ODD, and CD. These treatments vary in intensity dependent upon the severity of the disorder. Parent training is crucial as parenting practices, such as being too lenient/too strict, lack/excess of parental monitoring, poor parental role modeling, parental difficulties with stress management, lack of parental consistency, and/or developmentally inappropriate child expectations have a significant impact upon children's disruptive behaviors [12]. These behaviors also increase when children lack a routine, experience unexpected changes to routines, or when the child is tired, hungry, or ill. Parenting styles should be modified to be more effective, less critical, and enhance the parent–child relationship [12]. For minor behaviors, parents may ignore the behavior unless the child or another person is in danger and address the behavior once it has subsided. Children with verbal/physical aggression frequently misperceive events as intentionally aggressive, and treatment components are derived from this belief system. Cognitive components including increasing perspective taking, evaluating their contribution to events, improved communication skills, negotiation strategies, social skills development, and developing multiple, more efficacious methods to manage events. Behavioral components include working with the family to develop household/school/community expectations and consequences (positive and negative) for compliance or noncompliance with these expectations. Emotional components include learning methods to decrease symptoms of anger, such as progressive muscle relaxation and controlled breathing, and by increasing emotional range by identifying, labeling, and expressing emotions appropriately [13–16].

Temper Tantrums, ODD, and CD: Medication Management

At present, there are no medications that reduce the behaviors labeled as temper tantrums, ODD, and CD. However, medications may reduce symptoms of comorbid disorders, such as anxiety disorder or depressive disorder, which may affect symptomology. Providing medications that have abuse potential, particularly to those with ODD

and CD such as stimulants for ADHD, should be carefully considered.

Specific Phobias

Phobias are classified within anxiety disorders and are an unreasonable and disproportionate fear response to an item/event. There are several criteria for specific phobia, but no minimum criteria are required to meet a diagnosis.

Criteria include:

1. Anxiety regarding a specific item or event, in children this is typically manifested by crying, tantrums, immobilization, or attaching to a security figure.
2. The item/event typically elicits an immediate anxiety response.
3. There is an attempt to avoid the item/event or the item/event is tolerated with extreme anxiety.
4. The anxiety response is disproportionate to the realistic threat of harm to the item/event.
5. The anxiety response or avoidance of item/event is present for at least 6 months.
6. The anxiety response or avoidance impacts functioning across environments.

Types of specific phobias:

1. Animals (snakes, dogs, spiders, etc.)
2. Natural environment (storms, thunder/lightening, heights, water, hurricanes, earthquakes, etc.)
3. Blood-injection-injury (dentist, doctor, needles, etc.)
4. Situational (airplanes, elevators, etc.)
5. Other (clowns, darkness, vomit, choking, etc.) [1, 17]

Specific phobia may present after experiencing a trauma, observing others experience a trauma, experiencing an unexpected panic reaction to an item/event, or information transmission of an event. Children do not typically realize that the fear is unreasonable although older children and adolescents may recognize their fear response is disproportionate [17]. Prevalence rates of specific phobias are approximately 5 % in children and 16 % in adolescents [1]. Specific phobias typically present between 7 and 11 years of age and decrease with age but may remain present in adulthood [1]. Specific phobias are twice as common in females compared to males [1]. Females are more likely to experience animal, natural environment, and situational phobias compared to males [1, 17]. There are no gender differences in blood-injection-injury phobias [1, 17]. Rates of specific phobias are higher in children with first-degree relatives who also have a specific phobia diagnosis. Environmental influences include overprotective parenting practices, loss/separation from parental figure, child abuse and neglect, and past negative interactions with the item/event. Individuals with blood-injection-injury phobia are less likely to access necessary medical treatments. Individuals with specific phobias are at increased risk for experiencing difficulties in home, employment, and community activities.

Specific Phobia: Cognitive-Behavioral-Emotional Treatments

Cognitive-behavioral treatment (CBT) options are similar to those implemented for anxiety. Cognitive restructuring involves identifying negative thoughts regarding specific phobias, challenging negative thoughts with evidence, and changing the thoughts to be more accurate. Behaviorally, the child should receive instruction on relaxation techniques, such as controlled breathing and progressive muscle relaxation, to implement during exposure exercises and decrease physiological response to the phobia. Emotion regulation strategies include expanding emotional range (fear) from all-or-none thinking to understanding that emotions exist on a spectrum and, hence, emotional responses also exist on a spectrum. Once CBT and emotional regulation strategies have been mastered, a hierarchy of exposure exercises related to the specific phobia, ranging from minor to major, should be developed and implemented coupled with CBT strategies to desensitize the phobia [17].

Specific Phobia: Medication Management

There are no medications for specific phobias, and treatment options should primarily focus upon CBT options. If the child's specific phobia is present along with anxiety, then a medication may be considered once CBT methods have been implemented and residual symptoms remain. Often an SSRI may reduce symptomology. However, in children only fluoxetine is currently approved by the FDA, and there is concern for an increased risk of suicidal ideation/actions in this age group [12].

Tics

Tics are motor, vocal, or a combination of both and occur as a sudden movement or uttered sound during otherwise normal behaviors. Tics are often repetitive with multiple repetitions of the same movement or sound. They may be classified as simple, such as eye blinking or nose twitching, or complex, with a series of movements in the same sequence. Tourette's syndrome is the most severe of the tic disorders and involves motor and vocal tics. Children with tics usually have awareness of the urge to engage in the motor or vocal tic and may temporarily be able to suppress this urge. Prevalence rates of tics range from 5 % to 25 % in school-age children, with chronic tics occurring in fewer than 1 in 500 children. The age of onset is typically between 5 and 18 years of age and most commonly occurs between 7 and 10 years of age [18]. Tics wax and wane and generally tend to decrease with age. Rates of tics are higher in children with first-degree relatives who also have a tic disorder diagnosis. Tic disorders are more common in male children compared to female children. The age of onset, duration, frequency, and severity as well as whether tics are motor, vocal, or combined should be considered. These factors help determine whether tics are the transient type that occur in up to 25 % of children or are more worrisome. Early onset, severe, multifocal tics that cannot be suppressed are more likely to indicate a secondary cause and should be investigated. Motor and phonic tics may indicate Tourette's syndrome. Abrupt onset, persistent tics and those that are more severe should prompt a search for secondary causes. Most tics are mild in severity, but even mild symptoms can affect children across environments. Transient tics can occur in chronic tic disorder, postinfectious autoimmune neuropsychiatric disorder associated with strep or postencephalitis states. Tics often occur with ADHD and are also a common side effect of ADHD medication. Tourette's syndrome can be associated with behavioral problems, ADHD, OCD, and learning disabilities [18, 19].

Tics: Cognitive-Behavioral and Medication Treatments

Cognitive-behavioral treatments (CBT) may be helpful with or without the use of medications. Tics may be treated with typical neuroleptics such as pimozide (Orap) or haloperidol (Haldol), atypical neuroleptic/antipsychotics such as risperidone (Risperdol) or aripiprazole (Abilify), or some antihypertensives such as clonidine or guanfacine (Intuniv) [18, 19].

Stuttering

Stammering or stuttering is a speech flow or fluency disorder in which speech patterns are disrupted by involuntary repetitions and prolongation of sounds, syllables, words, or phrases as well as involuntary silent pauses or blocks during which the child is unable to produce sounds. The origin of stuttering is unknown, but causes may include stressful life events or lack of grammar skills. Stuttering may also result from medical conditions, brain injury or trauma, mental health problems, or emotional trauma. Stuttering usually occurs across home, school, and/or work environments. Stuttering disorder typically presents in childhood and may be transient or lifelong; 75 % of preschoolers who stutter report symptom remission as they age. Stuttering is four times more common in males compared to females.

Risk factors for stuttering include first-degree relatives with stuttering disorder, the presence of other speech or language disorders, and fear about stuttering on the part of the child or family. Stuttering increases in frequency and severity if the person is excited, tired, or under stress. In situations in which they may feel self-conscious, hurried, or pressured, the symptoms may worsen. Large groups or talking on the telephone may be difficult for many people who stutter. Children with stuttering disorder are at increased risk for academic (lower participation rates), emotional (low self-esteem), social (avoidance of speaking situations), peer (risk for being bullied, teased), employment (passed up for promotion), and psychological (difficult communication patterns, anxiety, phobia) impairment compared to peers without stuttering disorder [20, 21].

Stuttering: Cognitive-Behavioral Treatments

Goals of treatment include increasing the child's ability to speak fluently, communicate effectively, and participate fully in daily activities. A certified speech and language pathologist utilizing a series of standardized assessments should evaluate stuttering. Evaluations should include the frequency and timing of disfluencies, speech rate and language skills, and child reactions and coping strategies regarding disfluencies. Speech and language therapy teaches specific skills to improve oral communication including controlling and monitoring the rate of speech, practicing smooth fluent speech at a slow rate, and using short sentences and phrases. Follow-up and maintenance treatments are important to maintain treatment gains [20, 21].

Thumb-Sucking

Thumb-sucking is a developmental behavior found in infants. At birth, infants reflexively suck on objects placed in their mouths. Sucking during feedings provides pleasure, comfort, and warmth, and sucking on the thumb, finger, or pacifier becomes associated with a strong oral sensation of soothing and pleasure. Ultrasounds have shown thumb-sucking behavior in utero, as early as 15 weeks gestation. The sucking reflex disappears at about 4 months of age. Since thumb-sucking is not purely reflexive, so it may persist but typically resolves by 5 years of age. There are no differences in thumb-sucking rates between genders [22]. Children who suck their thumbs, especially older children, are at an increased risk for social (bullying, teasing), communication (deficits due to pronunciation difficulties), psychological (stress, anxiety), and medical (dental disorders, open bite, high-arched palate, and infections) problems compared to peers who do not suck their thumbs [22–24].

Thumb-Sucking: Cognitive-Behavioral Treatment and Medication Management

Dental evaluation and intervention of thumb-sucking is necessary if the permanent teeth are presenting and there is alteration in dentition or if the child is embarrassed by the habit. Dental interventions include the use of special mouth guards and over-the-counter products that are bitter tasting and can be applied to the nails to deter thumb-sucking. Cognitive-behavioral treatments (CBT) include identification and management of triggers such as stress or fatigue and offering the child an alternate comfort measure (hugs, reassuring words, pillow or stuffed animal). Furthermore, use of positive reinforcement (extra bedtime stories, reward board with stickers) in conjunction with verbal reminders regarding the behavior without scolding, criticizing, or ridiculing may reduce thumb-sucking. Use of a special verbal or physical signal when parents identify the behavior in public can help avoid embarrassment. Peer pressure may also assist with cessation of thumb-sucking in older children [22–24].

Nail-Biting

Onychophagia, or nail-biting, is a common childhood behavior that is difficult to modify. Approximately 23 % of 3–6-year-olds and 50 % of

10–18-year-olds in the USA engage in nail-biting at some time point. Most people cease biting their nails by 30 years of age without intervention [25]. Nail-biting is more common in males compared to females, especially after 10 years of age. Nail-biting is classified under obsessive-compulsive and related disorders [1] and involves putting the nail into the mouth so that contact occurs with one or more teeth. Mild forms have been compared to nervous habits such as fidgeting. More severe forms may result in physical damage and could be considered self-mutilating behavior. Nail-biting may occur in times of stress, excitement, boredom, or inactivity and may be an unconscious activity that occurs when involved in another activity such as reading, watching TV, or talking on the phone. Children with a first-degree relative who has a mental health disorder are at an increased risk for nail-biting. Nail-biting may be seen with other stereotypical behaviors including lip biting, bruxism, head banging, skin biting, and hairpulling. Nail-biting may be present in children with ADHD, ODD, OCD, separation anxiety disorder, enuresis, tic disorder, intellectual disability, major depressive disorder, and pervasive developmental disorder. Medically, nail-biting may result in infection around the cuticles, damaged or bleeding nails, damaged gums, and digestive system problems if the nails are swallowed. Prolonged nail-biting can lead to deformity of the nail from damage to the nail bed. In severe cases, the nail is bitten until it is lost, then the fingers are bitten, and the cuticle and nail bed skin is chewed [25, 26].

Nail-Biting: Cognitive-Behavioral Treatments and Medication Management

The majority of people who engage in nail-biting are motivated to treat this behavior and have often tried, without success, to stop nail-biting. Nail-biting is difficult to treat and medications and habit reversal treatments have not shown consistent long-term effectiveness. Cognitive-behavioral treatments (CBT) include identification and management of stressors, alternative behavior substitution, stimulus control therapy, keeping nails trimmed and filed, wearing gloves or adhesive bandages, snapping rubber bands on the inside wrist as a negative physical response, and identification and treatment of comorbid psychological conditions (anxiety, OCD, impulse control disorders) that impact symptomology. There are several over-the-counter products that are bitter tasting and can be applied to nails to deter from nail-biting behaviors [25].

Pica

Pica is a disorder characterized by the consumption of non-food items that do not have nutritional value and are not culturally sanctioned.

Criteria include:

1. Repeated eating of non-food substances (e.g., chalk, clay, cloth, coal, dirt, gum hair, metal, paint, paper, pebbles, soap, string, or wool) for at least 1 month.
2. The eating behavior is inappropriate to the patient's developmental level and is not culturally or socially supported.
3. If the eating behavior occurs in the context of another mental disorder (e.g., autism, intellectual disability, or schizophrenia) or general medical condition (including pregnancy), the severity of the eating behavior warrants additional clinical attention.

Pica is more common in children, pregnant women, and in low-socioeconomic populations. In children, there are no significant gender rate differences. Cultural practices may be associated with the ingestion of a nonnutritive substance. For example, in African cultures, the ingestion of kaolin (white clay) is common and is not associated with psychopathology. Depending on what is ingested, complications such as lead poisoning, infections, and bowel obstructions may occur. Pica may also occur with anemia or with lower than normal nutrient levels, and as such hemoglobin, iron, and zinc levels should be evaluated [27].

Pica: Cognitive-Behavioral Treatments and Medication Management

If the pica is not culturally based, treatment of any underlying nutrient deficiency is the first step in treatment. Once all nonpsychotic causes for pica are eliminated, the use of SSRIs may be considered. Positive reinforcement of normal behavior and aversion therapy has been used [27].

Sleep Disturbances

Sleep disturbances, including insomnia, nightmares, sleep terrors, and sleepwalking, are common childhood disorders. Prevalence rates vary, but estimates are that at least half of all children will experience a sleep disorder at some time [28].

Sleep Disturbances: Insomnia

Insomnia is defined as difficulty with sleep onset, sleep maintenance, and/or early wakening.

Criteria include:

1. Difficulty with one or more of the following:
   (a) Difficulty with sleep onset (in excess of 20–30 min to fall asleep)
   (b) Difficulty maintaining sleep, frequent awakenings with difficulty returning to sleep (awakening for 20–30 min and unable to return to sleep)
   (c) Early morning awakenings and difficulty returning to sleep (wakening at least 30 min earlier than expected, unable to return to sleep, and obtaining less than 6.5 h of total sleep)
2. Sleep difficulties cause significant distress across environments.
3. Occurs three or more nights weekly.
4. Occurs for at least 1 month (specify: episodic) or 3 months (specify: persistent).
5. Sleep difficulties occur despite having enough sleep time scheduled.
6. Insomnia is not better accounted for by another disorder [1].

Insomnia typically presents in early adulthood but does present in childhood and adolescence on occasion. Insomnia is more prevalent in females compared to males, and children with anxiety tend to have higher rates of insomnia. Insomnia can be situational or chronic with episodes of reoccurrence and is strongly influenced by environmental stressors. Children with insomnia tend to have poor sleep hygiene habits, including spending excessive amounts of time in bed not sleeping, inconsistent sleep schedule (lacks regular sleep-wake times), and napping during daytime hours [1, 28–30].

Sleep Disturbances: Sleepwalking and Night Terrors

Sleepwalking, night terrors, and nightmare disorder are classified as parasomnias and are reflective of central nervous system immaturity.

Criteria include:

1. Recurrent episodes of partial wakening from sleep, typically occurring in the first third portion of the sleep cycle, accompanied by one or both of the following:
   (a) Sleepwalking: Recurring episodes of leaving the bed while still asleep and walking around the room, house, etc. During these episodes, the individual has a "blank face," does not respond verbally to others efforts to communicate, and is difficult to wake.
   (b) Night terrors: Recurring episodes of extreme fear that occur while asleep and results in immediate wakening, usually with a frightening scream. Usually accompanied by physiological factors such as rapid heart rate, rapid breathing, and sweating. The individual is difficult to calm during these episodes.
2. Little to none of the dream sequence is remembered.
3. Amnesia to the event.
4. Disorder is not better accounted for by another disorder [1].

Sleepwalking

Sleepwalking episodes are typically brief, less than 10 min, but can last up to 1 h in duration. The primary diagnostic feature is motor movement occurring during a sleep phase, which usually comprises leaving the bed and walking around the residence, but on occasion leaving the residence has been noted. Upon wakening, the individual is initially confused but quickly regains appropriate cognitive and behavioral functions. While sleepwalking, children may engage in normal, daily activities. Prevalence rates of children with at least one episode of sleepwalking range from 10 % to 30 %, with 2–3 % of children sleepwalk frequently, and prevalence rates decrease with age. Rates of sleepwalking are higher in females compared to males. Rates of sleepwalking are higher in children with a first-degree relative with a history of sleepwalking and/or night terrors [1, 28, 30].

Sleep Terrors

Sleep terrors are typically brief, less than 10 min, but can last longer, especially in children [1]. During these episodes, the individual experiences intense fear, resulting in physiological and behavior responses. Their eyes are often open, giving the appearance they are awake when they are not. The child is difficult to awaken and/or comfort, and once awakened, they have amnesia or only fleeting images of the night terror. Typically, the child will sit up in bed and scream and cry inconsolably. They report a feeling of fear and desire to escape. Sleep terrors typically occur only once nightly although they can, on rare occasions, occur several times nightly. Sleep terrors are uncommon during daytime nappings. Sleep terrors are more common in males compared to females in childhood. Prevalence rates are 37 % at 18 months of age and 20 % at 2.5 years of age, and rates tend to decrease with age. Rates of sleep terrors are higher in children with a first-degree relative with a history of night terrors or sleepwalking. Children with sleep terrors are at increased risk for cognitive (poor concentration, academic underperformance), behavioral (falling asleep in class), and psychological (anxiety, depression, mood liability) impairment compared to peers without sleep terrors [1, 28, 30].

Sleep Disturbances: Nightmare Disorder

Criteria include:

A. Recurring episodes of lengthy, unsettling, and well-remembered dreams with typical themes including evading threats to well-being, sense of security, or injury that usually occurring during the second half of sleep.
B. Upon wakening, the individual typically becomes cognitively alert and is able to describe their nightmare in great detail.
C. Symptoms are not better accounted for by another disorder.

Prevalence rates of nightmare disorder range from 1 % to 4 % in preschool children, and rates increase in adolescence. Nightmare disorder is twice as common in females compared to males [1]. Age of onset is typically between 3 and 6 years of age with rates peaking during late adolescence and subsequently decreasing. Nightmares may occur several times nightly and also during daytime naps. Nightmares tend to be lengthy, intricate, and story-like sequences of dreams that the child is able to recall, appears realistic, and results in a negative emotional state. Nightmares typically involve some degree of fear and avoiding or coping with a perceived threat to safety. Children often experience mild physiological symptoms including increased heart rate, breathing, and sweating [1, 28–30]. Nightmare disorders increase with environmental, family, and community stressors. Children with fevers and sleep deprivation have higher rates of sleep disorders [1]. Children with nightmare disorder are at an increased risk for social (peer rejection), behavioral (daytime sleepiness, aggression, poor impulse control), psychological (anxiety,

depression), and cognitive (academic impairment, slowed reaction times, decreased memory, poor attention) impairments compared to peers without nightmare disorder [1, 28–30].

Sleep Disturbances: Cognitive-Behavioral Treatments

There are multiple cognitive-behavioral treatments (CBT) to reduce sleep disturbances. Prior to implementing CBT strategies, the child's sleeping environment and routine should be assessed. Information gathered should include sleep-wake cycles and nap times and is the child given adequate opportunity to obtain sufficient amounts of sleep with the presence of a bedtime routine that is calming and predictable, does the child have their own bed, and do they feel safe when they are asleep.

Cognitive factors, including acute and chronic psychosocial stressors, should be addressed including home, school, and community factors and children's perception of their sleep disorder. Behavioral factors include establishing and enforcing sleep-wake cycles that do not vary by more than 1 h daily, eliminating co-sleeping if present, minimizing or eliminating caffeinated beverages after lunchtime, engaging in calming activities 1 h prior to bedtime, modifying the sleep environment to be dark and quiet, eliminating the use of electronic devices 1 h before sleep time and no access to electronics during sleep times, and maintaining a sleep diary to assess for sleep patterns [29]. Emotional regulation components include teaching methods to self-soothe when frustrated or anxious such as progressive muscle relaxation and controlled breathing techniques.

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Musculoskeletal Problems of Children

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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 9–12 years old and boys 12–15 years of age, 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 nonaffected 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.

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

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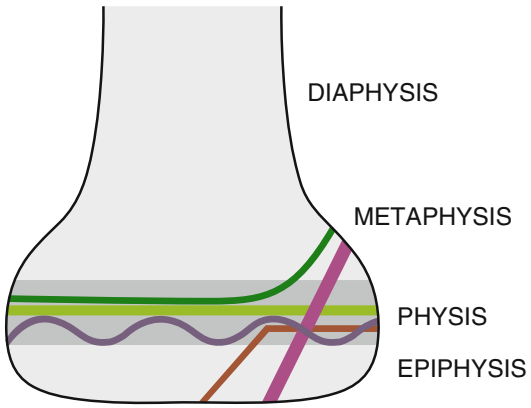

Fig. 1 Salter-Harris classification is defined by the location of the fracture relative to the growth plate (*the gray zone*). Type 1 (*yellow*) is a separation of the growth plate (*STRAIGHT across*). Type 2 (*green*) is a fracture ABOVE the growth plate into the metaphysis. Type 3 (*orange*) is a fracture 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)

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 re-fracture [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, 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.

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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

Stress Fractures

Stress fractures are most commonly seen in young females but may also affect males. 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 tissues, applying stress on the bone that is suspected to be involved may elicit pain, thereby making the diagnosis of stress fracture more likely. 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.

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 a bruise is present, an avulsion fracture should be suspected. Radiographs of the hip and pelvis 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. If limping is predominant, limitations on weight bearing can be made. Children and adolescents should be enrolled in a rehabilitation program

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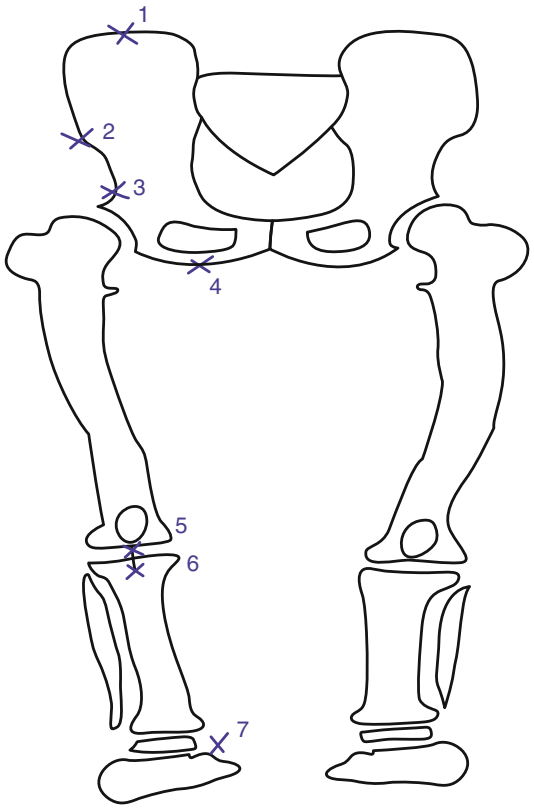

Fig. 2 Apophysitis locations. *1*. Iliac crest; *2*. Anterior superior iliac spine; *3*. Anterior inferior iliac spine; *4*. Ischial tuberosity; *5*. Inferior pole of patella (Sinding-Larsen-Johansson); *6*. Tibial tuberosity (Osgood-Schlatter disease); *7*. Calcaneus (Sever's disease)

focused on stretching and strengthening. 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].

Sinding-Larsen-Johansson Syndrome

Sinding-Larsen-Johansson syndrome is an apophyseal injury 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 towards 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 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

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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) who participate in sports which require a lot of running. The patient will often complain of unilateral or bilateral heel pain related to activity. Examination reveals tenderness of the calcaneal apophysis with weakened dorsiflexion and the gastrocnemius-soleus flexibility can be decreased. Imaging maybe done to rule out other conditions such as a unicameral bone cyst, if symptoms present unilaterally [14]. Management includes rehabilitation exercises and 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 inch heel lift with icing for 20 minutes 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 [15]. 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, with a prevalence of 3–37 %. These nonarticular leg pains occur at night in healthy active children 3–12 years of age, with a peak of 6 years [16]. 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

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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 kyphosis, and a family history of spondylolysis. These conditions are common among adolescent athletes with repetitive flexion and extension movements of the back, 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

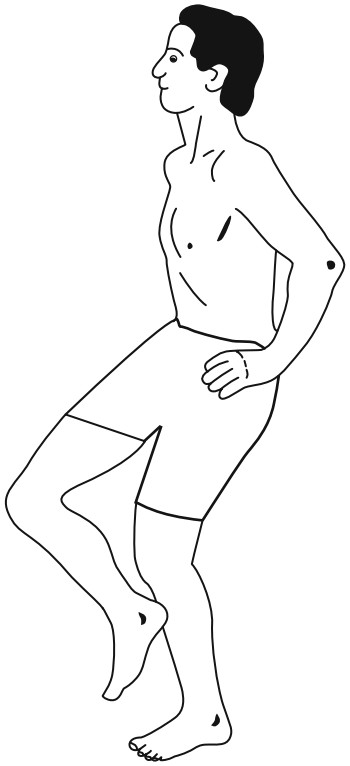

Fig. 3 The Stork Test: Ask the patient to lean backwards while standing on one leg; considered positive if the back pain is reproduced on the same side the patient is standing on

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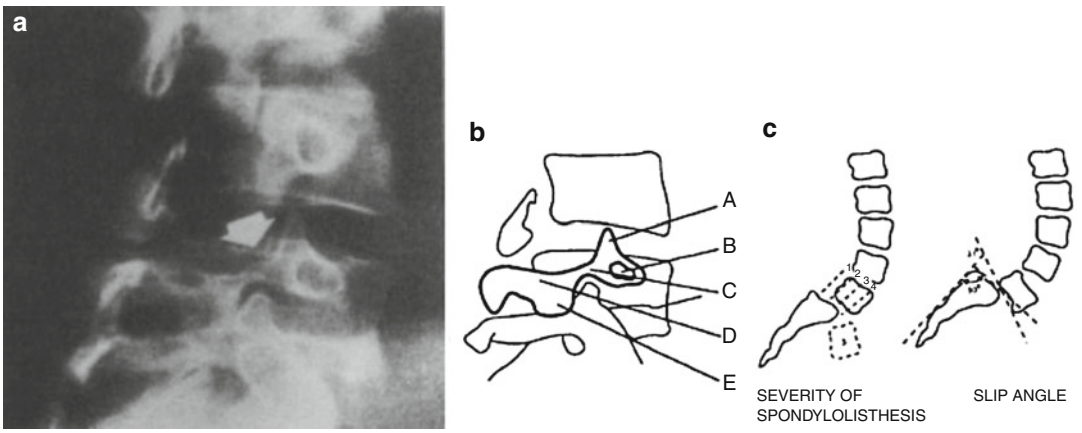

Fig. 4 Spondylolysis, and spondylolisthesis (*right*). (**a**) Radiographic representation of an abnormal elongation (*greyhound sign*) of the pars interarticularis, or the "neck" of a scotty dog (*arrow*). Other defects, such as sclerosis or lysis in the pars, are best visualized in this "neck." (**b**) "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])

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 thoracolumbosacralorthosis (TLSO) for pain management, and aggressive physical therapy. Treatment of spondylolisthesis will depend on the grading of slippage; however, early cases can 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].

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 ($\geq$10 years). These children may present after a school screening, which is currently not supported by the United States 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 Adams 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) [22]. Lateral bending films are sometimes obtained for pre-operative 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 [23]:

- 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

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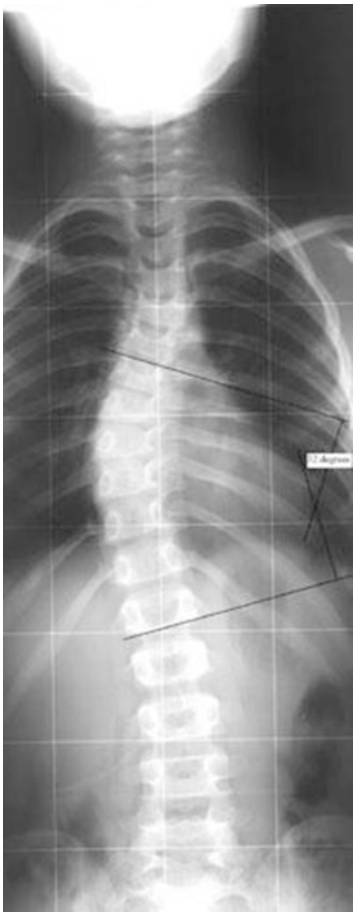

Fig. 5 Measurement of the scoliosis angle (Cobb 1948). Horizontal lines are drawn parallel to the endplates of the neutral vertebrae at the end of the curve. Where perpendicular lines intersect, the angle of scoliosis is measured. In this case, the angle of Cobb measures 32° (From Ludwig K., Nierhoff C [21]. With kind permission from Springer Science and Business Media)

- Any patient with a progression of 5° or more of the Cobb angle

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 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 [24].

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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 [25]. 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 show 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 "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 [26]. 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 [27]. 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 minutes after reduction. 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 the 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 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. 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

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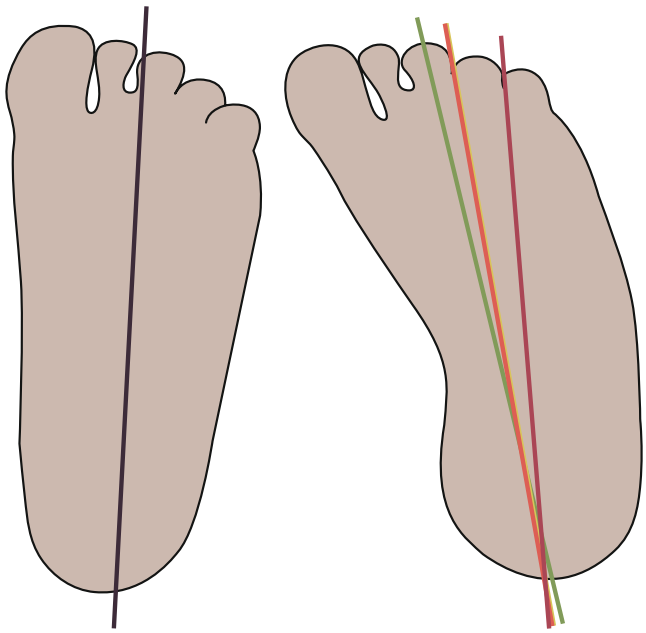

Fig. 6 Heel bisector method for determining metatarsus adductus severity. On the left, shows a normal heel bisector line drawn in black. On the right, a comparison of where the heel bisector line will fall in relation to the toes for mild (*green*), moderate (*orange*) and severe (*red*) metatarsus adductus

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 ten seconds. The parent should be instructed to perform it five times a day on each foot [28]. Severe cases that are rigid maybe 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 [29]. Only when the torsion is severe (TFA more than 85°) should surgical intervention be considered.

Femoral Anteversion

Children greater than 4 years old will commonly have in-toeing secondary to femoral anteversion. Sitting in the classic "W" position [30] with their knees together and feet on either side can contribute to the femoral anteversion. While walking, the child's legs appear 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 [31].

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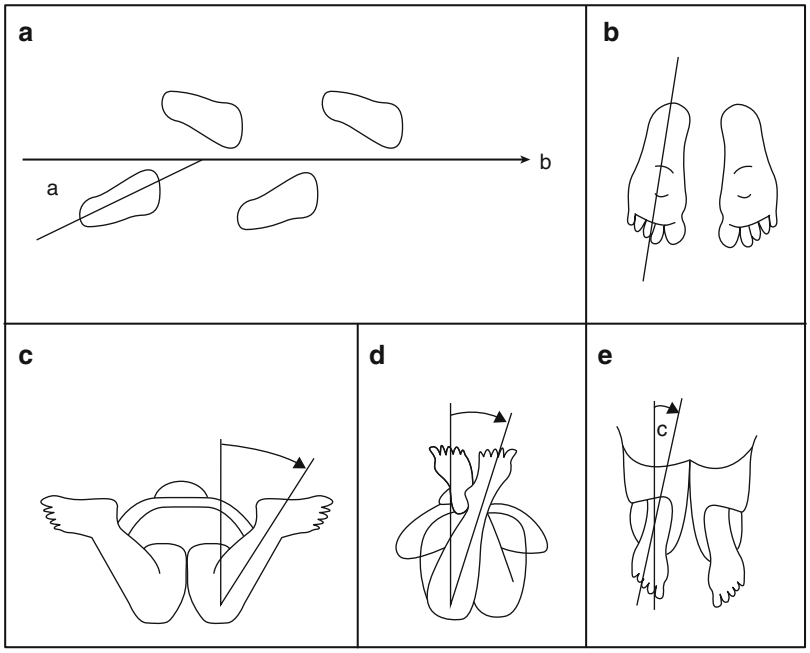

Fig. 7 Tests for torsional deformities. (**a**) Foot progression angle (*a*) is formed by the foot axis (**b**) and the line of progression (*b*). (**b**) Foot axis. (**c**) Measurement of internal femoral rotation. (**d**) Measurement of external femoral rotation. (**e**) Thigh-foot angle (*c*) is formed 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)

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 [32]. 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 [32]. The teleograms will show the bowing deformity of the proximal tibia and medial beaking, with a downward slope of the proximal tibial 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

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is warranted. In contrast, the adolescent form is more appropriately managed by an orthopedist because surgery is more likely as a possible 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 [32]:

- Unilateral genu valgum
- Height that is below the third percentile
- Greater than 8 cm between the medial malleoli when the knees are extended, patellas pointed straight, and the femoral condyles 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 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 re-evaluation of examination techniques suggests that Ortolani's test is more important [33]. In children over 3 months of age, DDH is highly suspected if passive abduction of the hip is less than 45° [34]. 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 positive if the knee of the affected side is lower than the other. The Klisic test is performed by imagining a line

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between the anterior-superior iliac spine and greater trochanter to see where if 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 [35]. 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 [36] (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 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 [37]. 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 [36] 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. influenza* type B, and *Streptococcus pneumonia*. 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 nonradiating, 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 [38]. 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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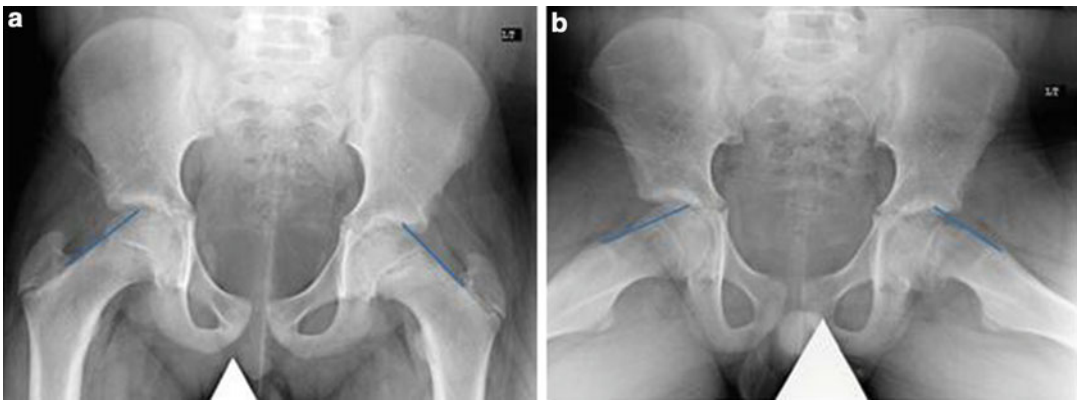

Fig. 8 Slipped capital femoral epiphysis. Image (**a**) is the anteroposterior (*AP*) view. Image (**b**) is the frog leg lateral view. The *blue line* on the AP (Klein's line) drawn along the femoral neck demonstrates the relative varus of the femoral epiphysis. A similar line drawn on the lateral demonstrates the relative posterior displacement of the left femoral epiphysis compared to the normal right hip (From Lee, M. [39]. With kind permission from Springer Science and Business Media)

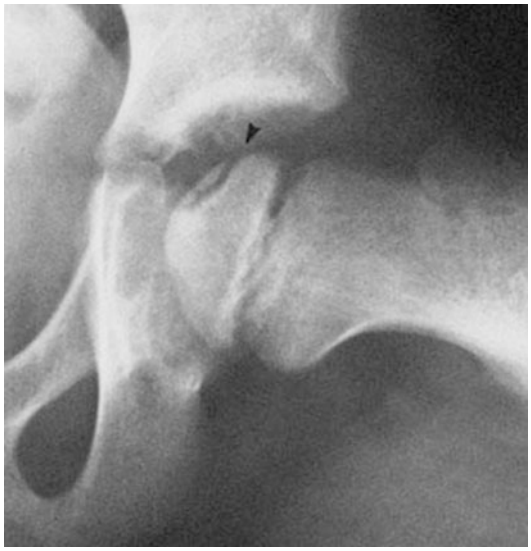

Fig. 9 Perthes disease lucent crescent (*arrowhead*) of the outer femoral head on a frog-leg view in an 8-year-old boy (From Oestreich AE and Crawford AH [40]. With kind permission from Springer Science and Business Media)

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.

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]. Orthopedic referral should be made for any child older than 6 years or children younger

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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) [41]. Containment treatment involves various methods of keeping the femoral head within the socket to allow remodeling of the femoral head as it heals.

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 a very common among newborns, secondary to the uterine positioning [1]. After birth, the foot appears hyperdorsiflexed with eversion. 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," can be caused by many etiologies, including congenital and neuromuscular disorders. 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 [42].

Pes Cavus

"Pes cavus" refers to abnormally high-arched feet. 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.

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Table 3 Orthotics for pes planus (flatfoot) [43, 44]

Stating Orthotic type	Type of Support Given
Internal heel wedges	Applied medial provide hindfoot inversion
University of California Biomechanics Laboratory (UCBL) orthosis	Provides longitudinal arch support by encompassing heel and hindfoot
Heel cup	Provides calcaneal support

Flexible versus Rigid Flatfoot

Parents are often concerned if their child's foot is flat. 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 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 towards 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 should be obtained to confirm the coalitions. If they are not well visualized, a computed tomography (CT) scan 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 most commonly affects the second metatarsal head but may also affect the third or the fourth metatarsal head [45]. 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, modification of activities may be sufficient. However, if the pain becomes particularly bothersome, short-term casting 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

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present with foot pain and limping. On examination, there is tenderness on 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 [46].

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Selected Problems of Infancy and Childhood

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Developmental Surveillance

The 1st year of life is marked by the highest rate of growth and development. The brain doubles in size in the 1st year of life and increases in size by another 15 % in the 2nd 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 5th 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.

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

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 exposures	Drugs and toxins: alcohol, illicit drugs, teratogens Congenital infections: (TORCH) Malnutrition (IUGR), placental insufficiency
Perinatal and postnatal conditions	Prematurity 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

delay is important in assessing the risk for developmental delays (Table 1).

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.

Assessment of development begins by obtaining history from the parents and should include soliciting concerns about their child's development, eliciting the history of developmental milestones, in addition to clinical observation of the child. Parental assessment of their children's development and concerns about the child's development have been shown to correlate strongly with the presence of developmental delay [4, 5]. Observation of the child–parent interaction is important in the assessment of children during developmental surveillance and may improve the identification of developmental delays. Examination of the child should include a comprehensive assessment. Growth pattern should be carefully assessed by studying the growth curve. Dysmorphic features or skin lesions should be noted.

The first step in evaluating developmental delay is to determine if the child has an isolated delay in one of the streams of development or a global delay affecting more than one stream of development. This will narrow the differential diagnosis and help in directing a referral if needed.

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).

Developmental screening instruments: the American Academy of 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 found that there is insufficient evidence to support recommendations for or against screening for autism or speech and language disorders [7].

Table 2 Normal Developmental Milestones

Age	Gross motor	Fine motor	Social emotional	Language
2 weeks		Coordinated and effective sucking. Hands fisted near face	Soothed by maternal voice and when picked up	Startles to voice
2 months	Lifts head off bed in supine position Head lag present	Hands fisted	Social smile	Coos in response to social interaction
4 months	Lifts chest off the table Steady head control when sitting No head lag when pulled to sit	Un-fisted	Laughs aloud with pleasurable interaction with parents	Vocalizes when alone
6 months	Tripod sit Leads with head when pulled to sit, Rolls over in both directions	Transfers object from hand to hand	Babbles, Gestures for up	Babbles interactively
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 Recovers to standing from stooping		Proto-declarative pointing: (points to share experiences with parent)	Uses 3–5 words, names 1 object Mature jargoning
18 months	Runs awkwardly Throws a ball Walks upstairs with hands held	Feeds self with a spoon	Points to 3 body parts	Uses 10–25 words. Names one picture on demand
24 months	Runs well Kicks a ball Throws a ball overhand	Follows a 2-step command	Parallel play	50 words or more, 2-word sentences, 50 % intelligibility, knows own name
30 months	Jumps in place Kicks ball throws ball overhand	Imitates horizontal line Takes clothes off	Imitates adult activities	Knows pronouns (refers to self as I) and prepositions (up, in, out)
36 months	Rides a 3 wheeler Catches ball	Copies circle Feeds self with a spoon	Starts sharing Knows name and gender	200+ words, 75 % intelligibility, 3-word sentences uses plurals, names body parts

Several developmental screening instruments are available. Developmental screening instruments have been found to be superior to clinical surveillance in the identification of children with developmental delays [8].

Repeated testing is important since some of the more subtle developmental delays may become apparent with time.

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

Management of children with a suspected developmental delay should not be delayed while a specific diagnosis is sought. 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 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

A thorough history including gestation history, perinatal history, and family history can provide important information. Prematurity is an important and common risk factor for developmental delays, with 11–12 % of babies in the USA born prematurely [9]. Therefore, premature babies require close developmental surveillance.

Physical examination should include documentation of growth parameters including the head circumference, assessment for dysmorphic features, and a detailed neurologic and developmental exam. It is important to remember that delays in achieving motor milestones can sometimes be caused by medical problems. These might include, for example, a delay in walking caused by developmental dysplasia of the hip, nutritional deficiencies such as rickets, or hypothyroidism [10].

The neurologic exam should assess for tone, reflexes, and motor or sensory deficits. Increased muscle tone is usually associated with central nervous system lesions, and neuroimaging should be considered. Decreased muscle tone in the presence of developmental delays may be due to hypothyroidism or muscle disease, and work up for these conditions may be indicated [11]. An increase in the level of creatine kinase (CK) indicates muscle disease and is the hallmark of muscular dystrophy in the context of motor delay [12].

Many genetic and metabolic conditions are associated with developmental delay that is detectable shortly after birth or may develop later in infancy with arrest of development or developmental regression. These conditions include conditions such as mitochondrial diseases or lipid storage diseases.

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 [13].

Speech Development and Speech Delay

Language development starting in the second half of the 1st year is largely dependent on the volume and quality of auditory input and 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. Evaluation of speech delay starts with the assessment of auditory input, including hearing tests and assessment of the social environment. Assessing the nature of caregiver interactions with the infant is a critical part of the evaluation of speech delay in infants. Mental retardation or cognitive disability, regardless of the cause, often presents with speech delay.

Evaluation of the child with suspected speech delay should include assessment for the presence of congenital and genetic syndromes. Many of these syndromes are associated with speech delay. Speech delay is also a common presenting feature of autism spectrum disorder (ASD) and may or may not be associated with cognitive delay. 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 [14].

Detection of receptive or expressive language delay should prompt referral to an early childhood intervention program. The presence of associated social skill deficits or other features of ASD should prompt a referral to a specialist in developmental pediatrics.

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.

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]. 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 health care 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 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 3).

Table 3 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

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].

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 4.

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

Table 4 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

modulating drugs is not recommended outside of research settings [19]. 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.

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 certain levels of lead leads to dysfunction in almost all organ systems in the body. Lead poisoning is particularly important in children, who are particularly susceptible to its toxic effects. Children have mouthing behaviors that increase their risk of ingesting lead particles in dust or on objects. Additionally, children absorb lead more readily from the intestine, especially when they are iron deficient, which is also common in early childhood. More importantly, the developing brain is highly susceptible to the toxic effect of lead even at low levels. Potentially, lead exposure can lead to 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 food canning process, certain pediatric population groups remain at high risk for lead poisoning, however. 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 $\geq$27 % of housing built before 1950
2. Populations in which the percentage of 1- and 2-year-olds with elevated blood lead levels is $\geq$12 %
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, daycare, or any other place the child spends any time in for lead. Finding of any source of lead should lead to proper treatment and abatement of the source of lead followed by follow-up of the blood level of the child to ensure that the levels decline. Any other children living in the same household should also be tested.

Blood lead levels above 45 mcg/dl should be treated [21, 22]. Treatment is through chelation. 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 might be helpful when managing these patients [23].

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Health Care of the Adolescent

W. Suzanne Eidson-Ton

Contents

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, sexual, and emotional 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 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 US can be found at: http://www.gutmacher.org/sections/adolescents.php.

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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 he/she tells the physician that s/he plans to hurt him/herself, someone else, or that someone is hurting her/him. 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.

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:

Greeting

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?

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 he/she 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, girls should be asked about breast development and menses. Boys and girls should be asked about 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, 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.

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 in general it 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? Do you like school? Why/why not? 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? Do you see yourself as a boy or girl? & ***Drugs/alcohol/tobacco*:** Do you know anyone who smokes? Do you smoke? (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 like hurting yourself?

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.

(Younger ~ 10–14): Do you find that you are attracted to any of your peers? If yes, are they boys or girls? Do you have a boyfriend or girlfriend? Do you ever touch physically? As below, if appropriate.

(Older ~ 15–21): Have you ever had sex? Do you currently? With boys or girls or both? Do you have intercourse? Oral, anal, vaginal? Barrier protection? Contraception?

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]. Health care providers can help teens understand how and be motivated to take risks in the safest possible ways. 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 girls and boys to screen for possible intimate partner violence (IPV) but also to counsel teens of both 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? (if appropriate) What happens when you and your girl/boyfriend argue or disagree? Do you ever feel controlled by your boy/girlfriend?*

Finally, when working with teens and their families, it is important to be aware that many adolescents may be LGBTQ (lesbian, gay, bisexual, transgender, or questioning [their sexuality]). For this reason, it is important to ask all questions around sex and sexuality in gender neutral terminology. Family physicians can help adolescents and their families understand that there is nothing wrong or abnormal about being LGBTQ. Unfortunately, LGBTQ 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 LGBTQ 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 LGBTQ adolescents can be found at http://www.lgbthealtheducation.org/wp-content/uploads/Module-4-Caring-for-LGBTQ-Youth.pdf. Other resources for caring for LGBT youth can be found at http://prh.org/teen-reproductive-health/arshep-downloads/#transgender.

The physical exam in adolescence need not be more invasive that 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 2011–2012, 20.5 % 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 an inspection of the breasts and genital region for Tanner staging and observation of any abnormalities. However, there is no reason to do a more invasive genital exam unless needed for diagnosis of abnormal symptoms. The USPSTF (U.S. Services Preventive Task Force) recommends against testicular exam for screening for cancer in adolescents. Similar 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

Table 1 Tanner stages for girls

	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 course	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]

Table 2 Tanner stages for boys

	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 courser	Some axillary and facial hair
Stage V	16–17	Adult in size	Adult in size	Full adult distribution	20 % at peak growth velocity

Adapted from Ref. [11]

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]

screen sexually active girls for gonorrhea and chlamydia, but this can be done with urine PCR testing, 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 girls in the USA and other developed nations are reaching these stages at earlier ages than previously, possibly related to more available calories [12] (Table 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 back, the physician should answer any questions the teen has and remind the patient about confidentiality and the services that he/she 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 11–12 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 http://www.cdc.gov/vaccines/schedules/.

Regarding immunizations, HPV vaccine requires particular attention. The current immunization rates are very low for both sexes. In 2013, 57 % of girls received one dose but only 38 % received the full 3-dose series. The rates were even lower for boys, at 35 % and 14 %, 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 recent 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. 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 2007 National Youth Risk Behavior Survey found that fewer than 25 % of high school students were meeting these physical activity recommendations. 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 [16]. 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 is also important for optimal cognitive function and emotional wellbeing as well [17, 18]. Parent/guardian (s) and teens should understand the relationship between diet, physical activity, and screen time and physical and mental health.

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 [19]. 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 for teens, these parenting strategies often are 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) [20]. Adolescents with parent/guardian (s) who parent in an Authoritative style have lower risk taking behavior and higher school achievement [20]. 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. Some examples of helpful websites are:

A Parent's Guide to Surviving the Teen Years at kidshealth.org/parent/growth/growing/adolescence.html. Communicating with Your Teen at ohioline.osu.edu/hyg-fact/5000/pdf/5158.pdf.

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 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 [20].

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 as well as 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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Selected Problems of Aging

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Contents

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. The fastest-growing segment of all age-groups is that of age 85 and above in the USA. 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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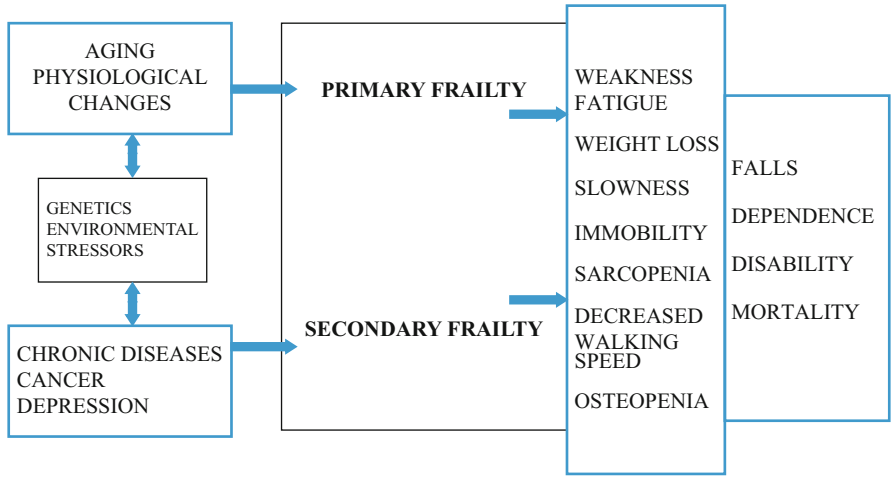

Fig. 1 Model for frailty

The overall prevalence of frailty in community-dwelling older adults aged 65 years and over in the USA ranges from 7 % to 12 %. This subset of the older population responds poorly to external stressors, lacking 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 in 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 there are altered 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. Of 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 a 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). The first manifestation of frailty tends to be weakness, slowed walking speed, and/or decreased physical activity. Walking speed has been shown to predict mortality, 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

Table 1 Frailty assessment tools

Frailty assessment tool	Content
Frailty Phenotype [40]	Uses signs and symptoms to assess by predefined criteria- Frail if 3of 5 criteria present
Clinical Frailty Scale [41]	Uses physical and functional indicators – 7 point scale to quantify degree of frailty
Vulnerable Elders Survey [42]	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 [43]	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 cut-off point for frailty
Edmonton Frail scale [44]	Multidimensional assessment instrument that includes the timed-up-and go test and a test for cognitive impairment
SHARE- FI frailty instrument [45]	Measures five items including grip scale- Has a web-based calculator
Tilburg Frailty Indicator [46]	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 [47]	Standard CGA-good correlation with clinical frailty scale
Frailty Index (Deficit accumulation Index) [48]	The Frailty Index is composed by a long checklist of clinical conditions and diseases. Score is based on total accumulated deficits
FRAIL scale [49]	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 %)

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

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.

Management

Frailty is managed by a team-based, multidisciplinary approach targeting biological, sociobehavioral, and environmental stressors and is associated with improved outcomes especially with respect to polypharmacy, falls, functional status, decreased nursing-home admission, and mortality [5]. Preventing and minimizing immobility and maintaining physical activity and muscle mass is critical in older adults at risk of frailty. Resistance, or strengthening exercise supplemented by aerobic exercise and balance training [6] (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 [7]. Addressing depression and various physical comorbidities is important to frailty management [8, 9]. Prescribing various appetite stimulants and anabolic agents to undernourished older adults needs further investigation. 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 [7].

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. 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.

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 Three medications associated with constipation

Anti-cholinergics -Tricyclic antidepressants
Anti-convulsants
Anti-hypertensives -Calcium channel blockers Diuretics
Anti-parkinsonsian drugs
Opiates
5-HT_3-antagonists
Nonsteroidal anti-inflammatories
Chronic laxative abuse
Bismuth, Iron, Lithium, Iron, Aluminum antacids

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 3 per week, for at least 3 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 [10, 11].

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 [10]. 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 perineal area, a digital anal 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 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 [11].

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, fresh fruits, and vegetables like prunes 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 and dehydration and rarely death. Lubricants are avoided in elderly as they can cause lipoid pneumonia if aspirated and 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 (Prucalopride) act by increasing intestinal motility and are available in Europe and Canada [12].

Sleep-Related Disorders in Elderly

Older adults consider quality sleep an essential part of good health [13]. Late-life insomnia is common in elderly. 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 [14]. 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) [15], periodic limb movement disorder [16], restless legs syndrome, and circadian rhythm sleep disorders. At least one-half of community-dwelling older adults use OTC and/or prescription sleeping medications [17].

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 [18].

Sleep-related disorders can be identified by routinely asking simple screening questions related to sleep habits, snoring, sleep quality, leg

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, non- absorbable, 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 one hour, 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 4 Tablets twice daily 10-mg suppositories or 5–10 mg by mouth up to 3 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		Not approved by FDA available in Canada and Europe

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 [9].

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 [9]. Short-term hypnotic therapy can be considered, but long-term use has been associated with increased adverse events like falls [19], cognitive impairment, and impaired driving [20, 21]. 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 [22]. OSA is also associated with motor vehicle crashes, and there is some evidence suggesting a link to cognitive impairment [23]. 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 health care system is organized in such a way that most sites of care like hospital, outpatient, and nursing homes work in silos and there is not much incentive to improve care coordination [24]. 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 health care system [25] (Fig. 2).

In acute care settings, systematic approaches using multicomponent multidisciplinary interventions decrease morbidity in hospital and improve functional outcomes [26–28]. In some situations hospital at home provides safe, economic, and effective alternatives to inpatient care in the community [9, 25]. Targeted interventions that improve care transitions before and after discharge, the use of home health services, caregiver support, case management, comprehensive discharge planning that includes follow-up, medication reconciliation, and education have all been shown to reduce in-hospital readmission and improve clinical and functional outcomes [25, 29].

The Program of All-Inclusive Care for the Elderly (PACE) [30, 31] is a model of care that provides inpatient, outpatient, and long-term services to frail community-dwelling adults requiring intensive care, typically only available in a nursing home setting. Interdisciplinary teams provide care across the continuum and cater to complex medical and social needs of the elderly.

Outpatient Comprehensive Geriatric Assessment (CGA) [26] and Geriatric Evaluation and Management (GEM) [25] 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 plans. 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 health care needs with the patient's primary care provider and community liaison [29, 31].

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. The goal for the physician is to assist the patient in finding the appropriate services and living arrangements (Fig. 2) [9, 32].

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

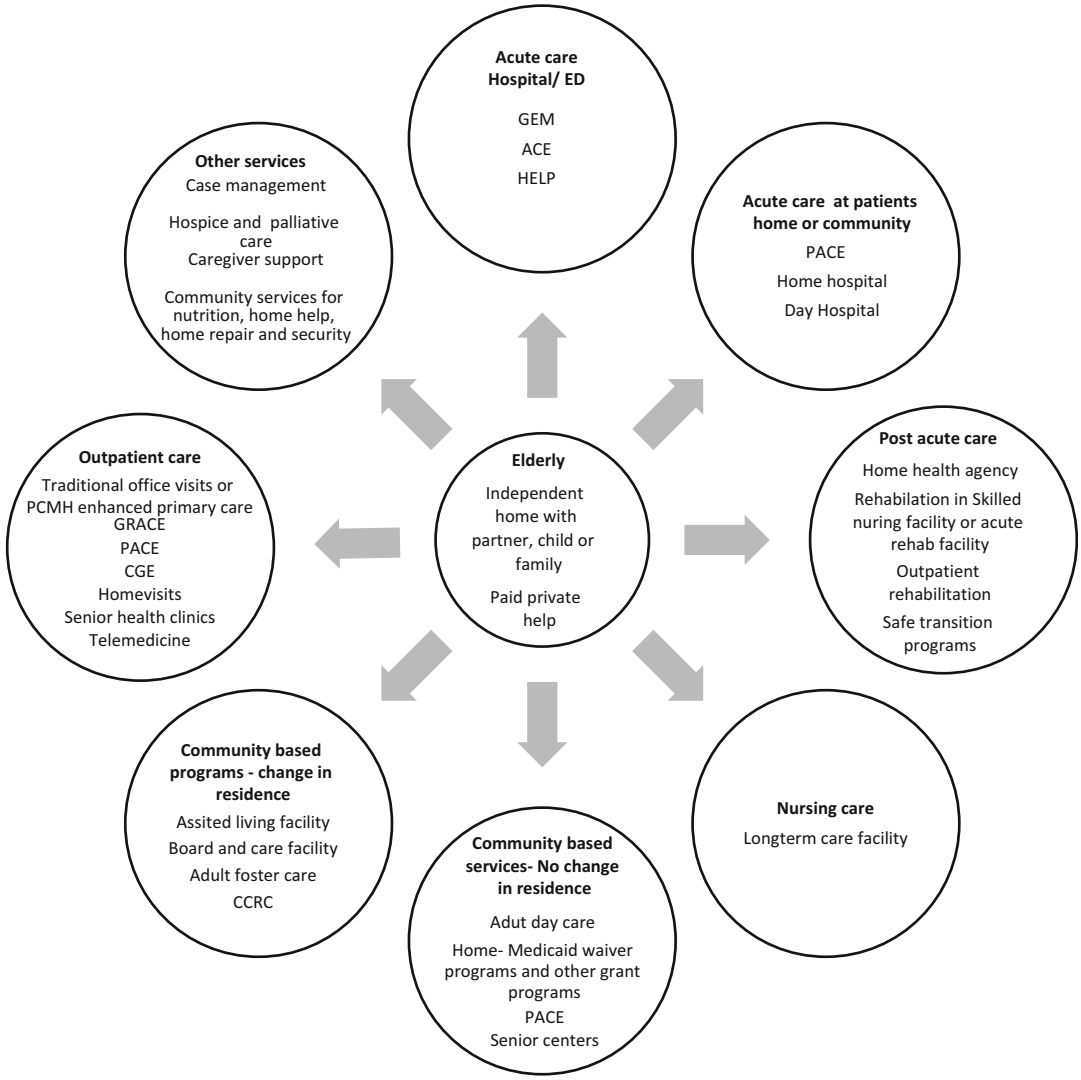

Fig. 2 Services available for elderly across various healthcare settings. *GEM* geriatric evaluation and management, *ACE* acute care of elderly, *HELP* Hospital elder life program

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

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. Non skilled 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 health care 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

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, 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 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 Centre 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 [33]. 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 [34].

The Affordable Care Act (ACA) of 2010 laid out several changes to the financing, coverage, and costs of health care for older adults. While the details will evolve over the years some of the major changes include creation of the Center for Medicare and Medicaid Innovation (CMI), 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 (beginning in 2014), in which many more Medicare beneficiaries will be qualified as dually eligible, eliminating many of their out-of-pocket expenditures.

Medicare Finances

In 2013, Medicare accounted for 14 % of the federal budget and 20 % of national health care spending, 23 % on physician services and 27 % of hospital payments. Of all Medicare revenue 89 % comes from people younger than 65 years old through taxes and interest on the Medicare trust fund, and only 11 % comes from monthly premiums, deductibles, and copayments. Total Medicare benefit payments for 2013 were 583 billion dollars [35]. Approximately 85 % of patients with Medicare have some form of supplemental insurance to help pay for deductible costs, copayments, and uncovered expenses (especially prescription drug costs). Of patients 15% 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 2010, the average Medicare beneficiary spent $4,734 out of pocket. This figure includes premiums for Medicare and other types of supplemental insurance and costs incurred for medical and long-term care services [36, 37].

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 copayments (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, or custodial nursing home care. The preventive services that are covered 100 % are yearly wellness visits, a fecal occult blood test, pap smear, Herpes zoster vaccination, screening mammogram, blood tests

Table 7 Six 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 health care	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 Starting in 2011, the coverage gap ("doughnut hole") will gradually be closed over the next 10 years. In 2012, beneficiaries will pay 50 % of the cost of brand name medications and 93 % of the cost of generic medications while in the coverage gap	Covers Hospital Part A and outpatient services Part B and drug benefits May have additional preventive services	Medicare supplemental insurance plan Pays copays 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	104–355 $ per month based on income	None	Varies 12–70 $ Plus plan premium based on income	varies	Varies by plan and health status
Deductible	1216 $ (may be covered by secondary insurer)	147 $ per year	None	Max of 320$	varies	varies
Other expenses	Pay partial or full after 60 days (unless dual eligible)	20 % copayments for some services	20 % copay in some states	Copay and copayments 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 vison, dental care or LTC

for diabetes and cardiovascular disease, and 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 [33].

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 84years. Older adult drivers have the highest fatality rate per crash and per mile driven among all age-groups. 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. 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 [38].

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 [39]. 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.

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")
Motor loss	Loss of grip strength and wrist function Limitations in rotation of neck Limitation in upper and lower extremity motion/strength
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

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Common Problems of the Elderly

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Elderly patients present a unique challenge to the family physician. They commonly present with multiple problems that are each multifactorial. A systematic approach is needed to assess and manage the common problems of the elderly. More complete reviews may be found in textbooks of geriatric medicine [1, 2].

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 [3]. UI affects 15–30 % of older adults in communities and 50 % of those in nursing homes [4]. In the hospital, the prevalence of UI in the senior population is less well reported and varies from 30 % to 60 %. 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, and reductions in quality of life. The estimated total national cost of UI in the United States in 2007 was $65.9 billion, with projected costs of $76.2 billion in 2015 and $82.6 billion in 2020 [5].

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 [6]. 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 [7].

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 [3]. For acute-onset cases of UI, there often is a treatable cause. The mnemonic “DIAPPERS” is used to recall possible causes of transient UI [8]:

*D*elirium
*I*nfection – urinary (symptomatic)

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*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

Established Urinary Incontinence

With established UI, 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 [7]. 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 [7]. 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 hypertrophy 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 have become fibrotic and replaced by connective tissue. Neurogenic causes include peripheral neuropathy from diabetes mellitus, pernicious anemia, alcoholism, and mechanical damage to the spinal nerves from a herniated disk, spinal stenosis, or a tumor.

Functional incontinence, the fourth type of UI, occurs in patients with normal urinary functioning. It may result from a decline in physical or cognitive functioning or may be a result of psychiatric illness.

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

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

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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 mental status changes. Alcohol and caffeine intake also should be noted. Additional history should be inquired regarding sense of prolapse, prior surgery, urinary tract infection symptoms, parity and mode of delivery, vaginal symptoms, and bowel habit and 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 in cognitive status, and medication changes is especially important [9].

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 [10]. 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

There are three main approaches to treatment of UI: behavioral, pharmacological, and surgical [7].

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 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). 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, which included 94 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],

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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 inhibitor finasteride (Propecia, Proscar) also can be quite helpful.

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 hypertrophy), surgery may be required (e.g., transurethral prostatectomy).

Falls

Falls are the leading cause of fatal and nonfatal injuries among the elderly in the United States. In 2012 alone, falls cost approximately $30 billion in direct medical costs. [12]. 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, 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 most 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 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” [13] mnemonic useful:

*S*ymptoms
*P*revious falls
*L*ocation
*A*ctivity
*T*ime
*T*rauma

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), 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 [14–16]. A comprehensive medication

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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 [17]. The 2012 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: anticonvulsants, antipsychotics, benzodiazepines, nonbenzodiazepine hypnotics, tricyclic antidepressants, and selective serotonin reuptake inhibitors [18]. 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 proper-gripped slippers. A cardiovascular examination should include assessment of heart rate and rhythm, orthostatic pulse, and postural blood pressure (prone and supine). 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 fingerbreadths or less suggestive of the presence of vertebral fractures [19]. Screening tools such as the Timed Up and Go test [20] can be used to predict risk of fall. 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 that the patient may have multiple types of dizziness. Cause of vertigo includes benign paroxysmal positional vertigo (BPPV). 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. If syncopal falls are suspected, referral to a cardiologist is recommended. 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, with supplemental vitamin D recommended. Hip protectors (devices that absorb and shunt the energy of the impact of a fall away from the greater trochanter)

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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 [21]. 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 offered. 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 [22].

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 [23].

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 minutes of standing or head-up tilt to at least 60° on a tilt table" ([24], p. 46). It is estimated to be present in up to 70 % of institutionalized elderly and 6 % of community-dwelling elders [24]. 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 BP. Generally the standing BP is measured at 1 minute (for screening purposes, a single 1-minute reading is usually sufficient) and 3 minutes 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]) if the above strategies are unsuccessful and there are no contraindications. See the Finding Balance website (http://www.findingbalancealberta.ca/intervention-a-management-of-medical-risk-factors-for-falls).

Polypharmacy

There are varied definitions of polypharmacy, from using inappropriate prescriptions to using five or more prescriptions. Depending on the definition, the incidence of polypharmacy varies from 5 % to 78 % [25]. Inappropriate drug prescribing may lead to avoidable adverse drug events (ADEs). ADEs should be considered to be the cause for any new 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, increase costs, and increase mortality. The annual costs of drug-related morbidity are estimated to be $177 billion in 2000 [26]. 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

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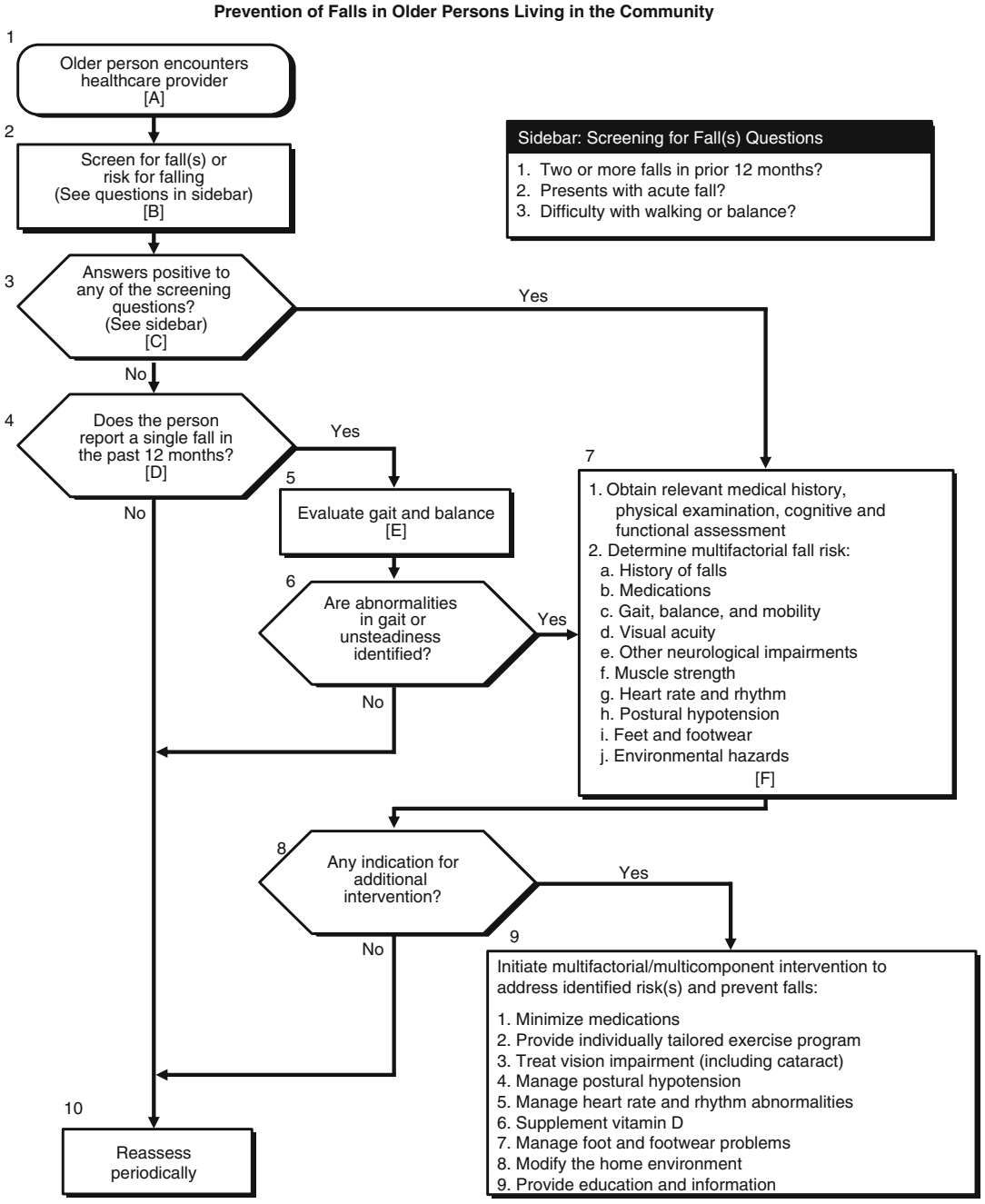

Fig. 1 Prevention of falls in older persons living in the community. This is an algorithm for screening and assessment of falls in older persons, developed by the Panel on Prevention of Falls in Older Persons of the American Geriatrics Society and British Geriatrics Society (Originally published in [18]; with kind permission of © John Wiley and Sons 2011. All Rights Reserved)

pharmacodynamics, increased comorbidities, polypharmacy, and nonadherence. Moreover, 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 2012 Beers criteria. It categorizes the medications/classes that should be avoided in those aged 65 years or older. It was developed from an interdisciplinary panel of 11 experts who applied modified Delphi method to the systematic review process and grading of evidence to reach consensus. Fifty-three medications or classes were identified and

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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. Some noteworthy additions of drugs to avoid in the 2012 Beers criteria include all short-acting benzodiazepines (regardless of dose), glyburide (DiaBeta, Micronase), megestrol (Megace), metoclopramide (Metozolv, Raglan), and sliding-scale insulin. New drug-disease interactions added include cholinesterase inhibitors in syncope, selective serotonin reuptake inhibitors in falls or fractures, and pioglitazone (Actos) or rosiglitazone (Avandia) in congestive heart failure [27]. There also is the Screening Tool of Older Persons' Prescriptions (STOPP) criteria [28].

Drug categories to avoid in the elderly, regardless of the consensus criteria used, include the following [29]:

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) not be prescribed for chronic usage
3. Anti-inflammatories (avoid chronic usage)
4. Opiate-related analgesics (e.g., pentazocine [Talwin], meperidine [Demerol])
5. Antiarrythmics 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 [30, 31]. 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.
   - Consider non-pharmacologic options.
   - 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) [32] is a regularly scheduled discussion between a patient and their doctor/pharmacist/nurse to 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

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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 2012 Beers criteria.
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").
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 [33, 34].
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 drugs from the same class or with similar actions.
8. Educate the patient/caregiver about each medication.
   - Know the patient's cognitive function, health literacy, access to care, and financial status/cultural factors/preferences.
   - Provide written information and engage in medication reconciliation ("teach me back" strategy).
   - Arrange a home visit to review medications with a transitional team member if needed.
   - Educate prescribers/MD.
9. Maintain the simplest medication regimen regarding number of medications, routes, and frequency of administration (once or twice daily dosing is best).
10. 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.
11. Use systems that support optimal prescribing behavior.
    - Drug utilization reviews.
    - Automated drug alerts providing information on potential drug interactions or dose problems.
    - Smartphone reference guides for drug-drug interaction tools.
    - Pharmacist-led interventions for medication review.
    - 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" [35, 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 [36]. 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, if not all, guidelines on drug prescribing are directed at single disease entities while older adults have multiple comorbidities. Pain and osteoporosis are commonly undertreated in the elderly.

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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 [37]. 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 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 [38]. 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], 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 pain is localized to specific joints, the alternatives to systemic NSAIDS are topical NSAIDs and adjuvant therapies that fit between nonopioids and opioids (e.g., tramadol [ConZip, Rybix, Ryzolt, Ultram]).

Opioids

Patients, including the elderly, who have pain most of the day, should receive their drugs regularly and not on an "as needed" basis (e.g., acetaminophen). 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 (Dolophine) 75–90 %, and for fentanyl (Sublimaze) 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. See the REMS website: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm.

Neuropathic Agents

For neuropathic pain, gabapentin (Gralise, Neurontin), pregabalin (Lyrica), or tricyclic antidepressants (TCAs) should be considered as first-line treatment. Serotonin-norepinephrine uptake inhibitors (SNRIs) should be considered first or second line. Gabapentin (Gralise, Neurontin) is effective for post-therapeutic 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 (Depacon), zonisamide (Zonegran), tiagabine (Gabitril), and clonazepam (Klonopin) should be considered second line, and the research for them is not as strong as

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Table 1 Opioid equianalgesic table [39]

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

for gabapentin (Gralise, Neurontin) and pregabalin (Lyrica). 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 [40]. 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, 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 nutrition due to impaired mobility or cognition.

Weight loss in older adults also 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 commonest cause of weight loss in the senior population (16 %), with depression the commonest (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 dementia. Conditions such as pressure ulcers, chronic infections, malabsorption, sepsis, malignancy, endocrine disorders, end-organ disease (e.g., congestive heart failure, end-stage renal disease, chronic obstructive pulmonary disease, hepatic failure), rheumatological disorders, and

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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 [41]:

*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)
*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. A weight loss as low as 5 % over 3 years is considered clinically significant 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 [32]. 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, experiencing less frequent hunger, and not regaining 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 include cancer, end-stage renal disease, chronic pulmonary disease, congestive heart failure, and 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 weights. 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

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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 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 clients 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 health illness; or 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 supplementation. These have been shown to increase weight (more so in patients at home or in long-term care) and to improve mortality except 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.

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 congestive heart failure and deep vein thrombosis is needed. Dronabinol (Marinol) has been shown to increase appetite in patients with AIDS.

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 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.

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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 tissue loss and fat may be visible.
Stage 4 – Full-thickness skin loss with exposed bone, tendon, or muscle.

Treatment of Pressure Ulcers

Prevention of pressure ulcers is focused on positioning and regular turning of bed- or chair-bound seniors at least every 2 hours. 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) [42]. Attention to pain control 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 [43]. 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. It also is important that caregivers receive support to ensure they can continue to provide care while also maintaining their own well-being.

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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. Things that elderly patients should consider in determining needs:

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 are available in many communities that allow patients to maximize their potential and function in their home environment for as long as possible. Community supports occur in many settings, such as faith-based programs, community-driven programs (e.g., leagues or groups), local programs (e.g., Seniors Association, 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 and homemaking services).

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. A mental status examination is important, as

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patients may appear relatively intact on casual questioning but actually suffer from severe cognitive impairment.

Home Living

Home living services provide home 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, 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.

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 facilities, residents pay an accommodation fee to cover the costs of providing accommodations and services such as meals, housekeeping, and building maintenance. Health services in long-term care 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. Recent evidence implicates the role of medical conditions more so than age-related changes [44]. 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 [44]. 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 – 9th Edition [45] and The American Medical Association Physician's Guide to Assessing and Counseling Older Drivers [46]). 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 use should be documented. Research has shown that

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benzodiazepines increase motor vehicular crashes (MVCs) by fivefold, antidepressants 1.8 times, and opioids 1.5 times [38]. 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. Recently, a paper and pencil test (the SIMARD MD) has been 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 [47]. Mandatory reporting of moderate to severe dementia is required in some US states and 7 of the 10 provinces and all three 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 such as the Department of Motor Vehicles on-road tests may fail to detect safety issues in this population of drivers due to overlearned skills [48].

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 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 not due to cognitive impairment or dementia, vehicle adaptations can be made to address this disability (e.g., peripheral neuropathy [foot drop]). Breaking bad news and driving cessation support programs have been developed and can be useful for patients and their families [49].

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Family Medicine
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Alzheimer Disease and Other Dementias

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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. 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.

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) [1]. 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 non-reversible dementias. A consultation should be considered if the diagnosis is in doubt.

Definition/Epidemiology

Estimates of dementia prevalence vary widely due imprecise diagnosis and documentation. Estimates on average 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 2013 there were approximately five million people in the USA with dementia. This number is expected to increase to 15 million by 2050 [3].

The 2013 revision of the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-5) introduced neurocognitive disorder (NCD), mild or major, to replace the diagnoses mild cognitive impairment (MCI) and 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 [4].

The diagnostic criteria for dementia are [4]:

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 a decline from a prior level of function.
3. Reversible causes of cognitive impairment including delirium have been ruled out.

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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 [2]
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 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

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 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) [5].

DSM-5 has added additional specifications for the likely etiology of the dementia (Table 2). 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 [5].

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. NIH recommends that these biomarkers not be used outside the research setting because there are currently no effective treatments to modify them and standardized interpretation guidelines are not fully developed [5].

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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 (Fig. 1)	
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 LBD and VaD, especially in older age groups (Fig. 1)
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 DLB, 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 %)	Caused by communicable pathogens, sometimes from cow brains, known collectively as prions. Creutzfeldt-Jakob disease (CJD) is the most common form
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

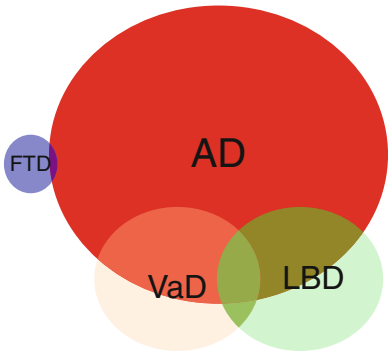

Fig. 1 Prevalence and overlap of common dementias. **Alzheimer's disease (AD) = 65–70 %. Lewy body dementia (LBD) = 15–20 %. Vascular dementia (VaD)- = 15–20 %. Frontotemporal dementia (FTD) = 5 %**

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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 though an autosomal dominant gene [6]. 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 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.

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 cognitive stimulation [7–9]. 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 [8]. 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.

The use of biomarkers such as amyloid PET scans to detect preclinical AD is not recommended as management would not change due to current lack of disease-modifying medical therapy. *ApoE4* gene presence is not a reliable predictor of AD and should not be checked.

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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 [5]. 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" ([10], p. 372). There may be a small subset of patients with clinically significant improvement. There was no significant difference between the CIs [10]. 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 [10]. CIs are used primarily for AD and LBD. They have no benefit in FTD, and they may even increase agitation [6].

Current guidelines suggest that these medications can be offered on an individualized trial basis if the patient/family desire it after discussion of their limited benefits, potential side effects, cost, and the patient's overall prognosis [10]. 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 [2]. A common conundrum involves a patient 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 [11]. 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 trail of discontinuing should be considered if these occur.

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 [2]. There is now an FDA black box warning for antipsychotic use for behavioral disturbances in dementia due to increased risk of death. 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 [12]. 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 [12]. 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. Other antidepressants may also be helpful if SSRIs are not effective or well tolerated. Tricyclic antidepressants should be avoided in most patients due to higher rates of sedating and anticholinergic side effects.

Benzodiazepines: These should be used with extreme caution due to increased confusion and fall risk [2]. 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 nonpharmacologic interventions.

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Table 3 Management of behavior 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
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 back-up 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

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. 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 [2].

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.

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 [13]. Prior discussion of the goals of care by the family

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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 [13]

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 [14] 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 [16]. 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 [17]. 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

physician is instrumental in avoiding non-beneficial and potentially uncomfortable and emotionally distressing interventions in hospitals or other settings as the disease progresses [14, 15]. 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 [18]. 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

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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.

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

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General Principles

Definition/Background

Elder abuse is defined by the National Center on Elder Abuse to be "any abuse and neglect of persons age 60 and older by a caregiver or another person in a relationship involving an expectation of trust" [1]. A growing body of literature shows that elder abuse is a significant problem throughout the world [2–5]. In the United States, the number of people over 85 years of age is expected to increase an estimated 400 % over the next 40 years resulting in a significant increase in the number of elder abuse cases [6]. For many abused and neglected older individuals, a visit to their family physician may be the only point of contact with a professional capable of identifying the problem and appropriately intervening.

Estimates regarding the incidence of elder abuse vary, in large part because of different reporting guidelines and research objectives [7]. Major studies have reported the incidence of elder abuse at 7.6–10 %, but when the more difficult to measure categories of financial abuse and self-neglect are included, the incidence is thought to be significantly higher [8, 9]. Disturbingly, it is estimated that 80 % of elder abuse cases went unreported to adult protective services (APS) agencies [7]. The risk of death among elderly individuals who experience abuse is three times greater than that of the general population [1]. Although the US Preventive Services Task Force found in 2013 that there was insufficient evidence to assess the balance of harms and benefits of screening all older or vulnerable adults for abuse and neglect, professionals in every state have a professional and legal obligation to report suspected abuse. Multiple agencies, including the Joint Commission, American Medical Association, and National Center on Elder Abuse, recommend routine inquiry about elder abuse [10, 11]. Only 2 % of cases reported to APS come from physicians, suggesting that physicians need to do a much better job of reporting elder abuse [12]. Increased physician awareness of the problem, knowledge of patient and perpetrator risk factors, and recognition of barriers to identifying elder abuse will increase appropriate physician intervention and decrease the sequelae of this condition.

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 treatment and prevention strategies.

Abuse Categories

Commonly used definitions related to elder abuse and neglect are as follows: [13]

Physical abuse: Willful infliction of physical pain or injury.
Sexual abuse: Nonconsensual sexual contact, including rape, unwanted touching, sexual advances, or innuendoes.

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Psychological abuse: Conduct resulting in mental or emotional anguish. This includes threats to institutionalize or withhold medication, nutrition, or hydration.

Financial or material exploitation: Misappropriating an older person's assets for someone else's benefit. Examples include theft, fraud, blackmail, and coercion.

Neglect: Failure to provide the goods or services necessary for maintaining health and avoiding harm or illness. Neglect can be active, such as intentional refusal to provide for basic needs associated with activities of daily living (hygiene assistance, medications, food), or it may be passive and unintentional, which can be the result of caregiver ignorance or inability to provide for the patient's basic needs.

Self-neglect is frequently omitted or reported separately in statistical summaries. Self-neglect has been described as "behavior of an elderly person that threatens his/her own health and safety" [14].

There is some disagreement in the literature as to the most common form of elder abuse. However, the available literature indicates that all forms of elder abuse are very underreported, in particular psychological [15], financial [16], and self-neglect [17]. In general, race- and ethnicity-based differences have not been observed in studies, with the exception of higher rates of physical mistreatment among nonwhite older adults [18]. It is important to recognize depression as a precipitating cause of self-neglect. Emotional abusiveness is considered foundational to most other forms of elder abuse [3].

Risk Factors

There are a number of characteristics common to victims of abuse and neglect. These include cognitive impairment, functional dependency, poor physical health or frailty, low income, trauma, behavioral problems, psychiatric illness or psychological problems, and past abuse [19, 20]. Cognitive impairments greatly limit an individual's ability to care for themselves, impair their decision-making capabilities, and limit their autonomy – all of which are risk factors for being victims of abuse. Identifying individuals with early-onset dementia is a very important component of any geriatric assessment [7]. While cause and effect relationships are difficult to establish, there does appear to be a significant association between the presence of a psychiatric illness and elder abuse [8].

An awareness of characteristics for those who are at risk of abusing or neglecting others is important for family physicians. Those include male sex of the caregiver, financial dependence on the victim, a history of violent acts, a history of substance abuse, and a current or prior history of psychiatric disorders [19]. Caregiver burnout is another important risk factor which family physicians, who often care for the entire family, are in a better position to notice than other healthcare professionals [7]. While caregivers may be able to cope with day-to-day demands, they may decompensate when a crisis develops or may become exhausted over time [7]. Arranging for supportive services to assist caregivers will help the entire situation including decreasing the risk of elder abuse. Because of significant dependence upon others, nursing home patients are particularly vulnerable to abuse and neglect [21]. Evidence supports a multifactorial etiology of elder abuse involving risk factors associated with the elder person, the perpetrator, their relationship, and environmental factors [19].

Identification Barriers

Patient Related

Although there is a relatively high level of awareness of the term "elder abuse," a large proportion of elderly individuals do not associate abusive behaviors in their personal lives with elder abuse [22]. It is not

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uncommon for elderly people to rationalize day-to-day infringements of their rights as "minor" violations that seem inoffensive when compared to the "real" acts of violence reported in the media [23]. Coping strategies identified in elder abuse patients include hope that the relationship with the perpetrator will improve [24]. A challenge in diagnosing elder abuse is that risk factors for abuse, such as social isolation and cognitive impairment, are also barriers to making an accurate diagnosis. Cognitive impairments may prevent individuals from recognizing the abusive nature of their situation [7]. Many elderly abuse patients are dependent upon caregivers or other individuals for transportation and/or assistance with activities of daily living. They may worry that reporting mistreatment will only make matters worse or result in nursing home placement and therefore not talk about their concerns with their primary physician [7]. Patients with early dementia may suffer from paranoid delusions, leading the physician to suspect abuse or, alternatively, inappropriately dismiss a patient's reports of abuse. Every effort should be made to provide appropriate treatment and also to ensure that elder abuse is not occurring despite suspected or actual delusions.

Physician Related

Physician barriers to reporting elder abuse include a lack of clinician education and comfort regarding the subject [25]. Poor understanding of the risk factors for elder abuse results in physicians having decreased ability to recognize elder abuse [26]. Physicians underestimating the prevalence of elder abuse, not knowing how to assess abuse, and not having developed a systematic plan to respond to elder abuse are also barriers [26]. Physicians may be concerned that reporting elder abuse can impair the physician-patient relationship, potentially decrease the patient's quality of life, and decrease the physician's ability to decide what is in the best interest of the patient [27]. Professionals struggle with ethical dilemmas created by elder abuse, especially when the victim does not want to cooperate with an investigation [28]. Family physicians however must be aware that they can potentially greatly assist a victim of elder abuse through appropriate interventions.

Assessment

Appropriate assessment of elderly patients suspected of being abused includes a careful history and a targeted physical examination. Although it is important to have a low threshold for suspicion of elder abuse, it is important to also note that a number of medical conditions can mimic abuse in older persons. These include allergic reactions, osteoporotic fractures, vaginal bleeding due to atrophy, and anorexia caused by mental illness [29]. Whenever possible, the initial portion of the history should be taken with both the patient and caregiver present. This allows for the physician to observe their relationship, with particular attention given to anxiety on the part of the patient or an overbearing attitude on the part of the caregiver [7]. Observing the caregiver and patient interaction can help in assessing if elder abuse is occurring. A potential red flag for possible elder mistreatment is a caregiver who often interrupts the patient to answer for him or her; however, such behavior does not always indicate elder abuse and instead may be helping to compensate for the patient's cognitive impairment [29]. Defensiveness and/or irritability of the caregiver may be a sign of burnout [30]. The physician should begin by asking open-ended questions such as "Can you tell me what happened?" [29].

Following the interview with both the patient and caregiver present, the patient must be interviewed privately [29]. Information should be obtained regarding current health status, living arrangements, financial status, emotional stressors, and social support. A history of alcohol and drug abuse, for the patient as well as other members of the household, should also be included [31]. A sexual history for any unwanted advances or sexual contact must be obtained [29].

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Anyone suspected of being abused should have a comprehensive physical examination. The patient should be completely undressed for the examination in order to perform a full dermatological evaluation. General signs in an elderly individual that suggest abuse include appearance of poor physical care and signs of psychosocial distress. Particular attention should be given to the patient's general appearance, skin integrity, neurological status, and musculoskeletal and genitourinary systems [29]. A complete skin examination is very important and should include an evaluation for bruising on flexor surfaces, bruising at different stages, and burns or other signs of unexplained trauma [32]. Two-thirds of injuries that occur in elder abuse affect the upper extremity and maxillofacial region [33]. Assessment of neurological status is also important, with special attention to cognitive function. Assessment of ambulatory skills is important in helping to ascertain if injuries from reported falls are consistent with the history or more consistent with abuse. Musculoskeletal examination should consider possible signs of injury that cannot be explained by the patient's history. A thorough forensic examination should be performed by someone trained in the evaluation of victims of sexual assault when that is suspected [34].

No consensus currently exists for a single standard algorithm for the evaluation and management of elder abuse [29]. The Elder Abuse Suspicion Index (EASI) is a screening instrument that can be used in cognitively intact patients, has been tested in the clinical setting, and has a sensitivity of 0.47 and a specificity of 0.75 [35]. The EASI has five patient-answered questions and one physician question. If cognitive function is impaired or unknown, initial screening with an instrument such as the Mini-Cog or Mini-Mental State Examination is recommended [29]. If cognitive dysfunction is confirmed, then further assessment should be performed to clarify the cognitive impairment prior to screening for abuse since the answers to questions might not be reliable [29]. Research is being conducted to develop effective, proven protocols which will improve the ability to accurately diagnose and assess elder abuse [29].

It is very important to document all findings when elder abuse is suspected. In addition to the routine detailed clinical note, documentation, including a diagram of all injuries and pictures if possible, should be included [7]. Radiographs should be obtained when possible if fractures are suspected along with a CT scan if the patient suffered a head injury. If clinical findings suggest malnutrition, then laboratory testing (e.g., complete blood count, blood urea nitrogen, creatinine, total protein, and prealbumin and albumin levels) should be requested to document findings consistent with malnutrition [7].

Management

Whenever feasible, the physician should discuss any concerns related to suspected abuse or neglect directly with the patient. Hospitalization of the patient may be necessary to provide treatment and protection pending further evaluation or legal investigation [29]. Family physicians may need to involve Adult Protective Services (APS) and other local services as part of a multidisciplinary approach to assisting elderly abuse patients [29]. Possible interventions include changing the patient's living situation to a nursing home, to a board and care facility, or with another family member if possible. A conservatorship can be prepared for patients with dementia. In a conservatorship, a person is appointed by a judge to protect and manage the financial and/or daily life of a patient with significant physical or mental limitations. Hospital social workers and case managers can offer significant assistance and are generally knowledgeable regarding available community resources. Continued involvement of the family physician even after the patient has been referred to an outside agency can greatly improve outcomes.

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Prevention

Prevention of elder abuse begins by being aware of the risk factors for elder abuse, allowing the family physician to better identify those at risk. Family physicians who have developed long-term relationships with patients and their families have a distinct advantage in assessing and addressing patient as well as caregiver risk factors [7]. Home healthcare professionals can further improve this assessment by observing both the elderly patient and the caregivers in the home environment. Collaboration between the office and home-visit information can be very useful in identifying situations at high risk for development of elder abuse as residents of assisted living facilities often have a poor awareness of available supportive services. Improving awareness of these resources could be a strategy to decrease the frequency of elder abuse [36].

Community Services

It is important to use a multidisciplinary approach that involves coordination with professionals from community agencies trained to deal with abuse and neglect situations from both the medical and social perspective. An awareness of the resources available in one's community is critical to making these connections. Online resources are available to assist physicians with elder abuse and include the Administration on Aging, American Medical Association, and Eldercare Locator [29].

Reporting Guidelines

Unlike child abuse, where legal statues clearly protect the rights of minors, elder abuse happens to adults who are usually presumed to be legally competent to make autonomous decisions. While it is important for this autonomy to be respected, physicians must also balance this right with the potential risk of injury and other complications if the suspected abuse is not reported [7].

All states require healthcare professionals to report suspected elder mistreatment [37], but the pertinent statues for elder abuse vary widely [38]. Reports made in good faith are protected from civil liability. Failure to report, however, can be considered negligence and is potentially punishable by fines, imprisonment, or loss of license.

An effective approach to reporting elder abuse includes working with adult protective services, having an accurate and accessible directory of community resources, and providing educational material for patients and families that includes a description of the warning signs of caregiver stress and available community supportive services [26]. By following guidelines for the detection and management of suspected abuse, physicians can improve their care for elder abuse victims and reduce the potential conflict between family members and the legal system.

Conclusion

A 2005 survey of family physicians and internists found that 80 % of respondents did not recall any medical school or residency training in how to diagnose and address elder abuse [39]. Proper care of elderly individuals at risk for abuse can and should be provided by family physicians. An awareness of the risk factors, barriers, signs and symptoms, and management approaches to elder abuse by primary care physicians can potentially help many patients in need.

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Child Abuse and Neglect

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Introduction and Approach

In 2012 there were 3.4 million cases of child abuse or neglect reported to agencies in the United States. Of this number, the majority were related to neglect (78.3 %), 18.3 % to physical abuse, and 10 % to sexual abuse [1]. The estimated cost of child abuse and neglect in the United States is 124 billion dollars [2]. While recent research suggests some reductions in the incidence of abuse and neglect, the occurrence of child maltreatment remains a major public health concern, both because the incidence remains high and because of the potential long-term implications for the physical and mental health of victims of abuse. Children under 1 year of age are most likely to be victimized. Children under the age of 3 are at greatest risk for death due to maltreatment or neglect. Children of African-American or Native American heritage are at greatest risk of victimization [1]. Approximately 47 % of all victims are under 5 years of age.

Risk factors that may place a child at increased risk of abuse include caregivers living in poverty, caregivers suffering from mental health problems or drug abuse, and domestic violence in the home. Characteristics of children who are more likely to be abused include those suffering from a disability, chronic illness, behavior problems, or a child who is a premature infant [1].

Child maltreatment is classified as abuse (physical, sexual, emotional, and others) or neglect. Definitions for what constitutes each of these areas are made by federal agencies and defined by each state (including each Indian Nation). It is important for the physician to be aware of the rules and laws for the jurisdiction in which they practice or to have a resource to discover this information if needed.

Mandated reporting, likewise, is defined and legislated by each state and includes professional reporting requirements in each jurisdiction and the method of reporting (phone call and/or written report) and also the time frame required for reporting. It is the responsibility of the physician to know what the laws are for the state in which they practice. The physician is generally provided immunity from legal risk if the filing of suspected abuse is carried out as specified in the state's requirements and for the safety of the child.

There are many reasons that providers have difficulty in differentiating abuse from other causes. First, there are many medical conditions that can mimic abuse such as toddler fractures, lichen sclerosus, and metabolic disorders. Second, many of the "injuries" are unwitnessed, and therefore, the cause of the injury is unknown. Third, children heal much more quickly than adults, so the injury may completely resolve or change dramatically over the course of several days before the physician has an opportunity to examine the child. And lastly, some children either lack the vocabulary skills to offer an explanation or are not ready to disclose at the time of the event.

Offenders are most often people who have contact with or access to the child; 80 % of offenders are parents [1]. Women are the perpetrators 53.5 % of the time. Most offenders are between the ages of 18 and 44. While assessing a child's injury, the physician must keep in mind that the offender may in fact be one or both of the caregivers accompanying the child to the exam. If it is determined that abuse has occurred, determinations and arrangements for custody of the child are the responsibility of law

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enforcement and child protective services. Prior to the victim leaving the provider's care, that decision should be made and documented.

A child's disclosure of abuse is a statement, drawing, or other means of communication about the abuse or neglect that he or she has experienced. Disclosure is often delayed for a variety of reasons. These include fear of retaliation, failure to understand the import of events, bribing or grooming by the offender, and fear of not being believed. It is important to appreciate that disclosure to the provider may be the only evidence of maltreatment. Verbatim documentation in the medical record of the statements made by the child to the provider is critical. Always consider that multiple types of abuse may have been inflicted on the child.

All children who are victims and over 4–5 years of age should undergo a brief mental health screen to determine the risk of self-harm.

If abuse or neglect is discovered, other children in the environment must also be considered to be possible or potential victims, requiring a safety plan and evaluation.

The effects of maltreatment can include acute problems such as a fracture, organ injury, or burn. At the time of the exam, there may only be limited findings, particularly in an infant or small child, and not be apparent until a later time manifesting as a behavior, learning disability, or another health issue. The Adverse Childhood Experiences study [2] has shown that repeated childhood exposure to adverse events such as physical, sexual, or emotional abuse can substantially increase the risk of future health problems. These include high-risk behavior (drug abuse, sexual activity, law violations) as a teenager, mental health disturbances as an adult (PTSD, depression, anxiety, chemical dependency), and physical health problems (chronic lung disease, ischemic heart disease, cancer, and others).

Physical Abuse

Physical abuse may present as bruises, burns, fractures, head trauma, or other injuries.

It is important for the physician to recognize the limits of the physical examination in young children. For example, due to the relative elasticity and deformability of their bones, fractures cannot be excluded without obtaining radiography in children under 2 years of age. In children under a year of age, a normal neurological exam is not sufficiently sensitive to rule out intracranial injury.

Bruises

A bruise age cannot be determined by examination [3]. The color of the bruise does not determine the age of the bruise accurately. Any bruise should be recorded in the physicians' notes and include comments on color, size, shape/pattern, swelling, tenderness, underlying bony elements, and absence of bruising in other areas such as normal trauma/contact areas for that child's developmental abilities. Past history should include a family history (genetic disorders, bleeding disorders), history of easy bruising, surgical bleeding problems (circumcision), medications, etc. A patterned bruise is very suspicious for an inflicted injury. The pattern may be consistent with the history (a slap causing outline of fingers, solid circumferential bruise with grab/choke) [4]. The absence of bruising, such as inside of the gluteal crease, may reflect a child's anticipation of, and response to, being struck, as opposed to an accidental explanation for buttock bruising, such as a fall. The examination should carefully look for physical findings to suggest other disorders, such as Ehler-Danlos or Menkes' syndromes [5].

Victims of abusive bruising are at significant risk of associated fractures (28 %). Children under the age of 2 should have a radiological evaluation, regardless of the physical exam findings.

Any follow-up care should note the presence or absence of new bruising after the victim is placed in a safe environment.

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Workup for bruising injuries should include:

1. Child under the age of 2: Radiological skeletal survey and repeat skeletal survey in 2–3 weeks [29]. A non-contrasted CT of the head should be obtained on any child suspected of having an inflicted head injury and those below 6 months of age with any inflicted injury. If the CT is positive for signs of trauma, a dilated eye exam should be obtained. An MRI of the head might also be considered.
2. Child over the age of 2: Consideration of radiographs of specific bones, consideration of CT or MRI of the head if indicated from the history or physical exam.

Laboratory testing to consider might include a PT, PTT, and CBC with platelet count, von Willebrand panel, and possibly platelet function testing. Hematology consultation might be considered if abnormalities are noted on these tests. If there are concerns for an abdominal injury, appropriate radiological studies (usually CT with intravenous contrast); liver enzyme, amylase, and lipase tests; and urinalysis might be considered,

Burns

The differential diagnosis for a burn is very similar to bruising, in which the differential can extend to conditions that include genetic, infectious, accidental contact, or medication causes [3, 6]. The provider must consider the developmental abilities of the child in the evaluation (a toddler reaching into hot water, school-age child playing with lighters/matches) and gather information regarding the injury including clothing worn at the time, position of child (standing, sitting), the type of agent causing the burn (solid, water, viscous fluid, cold exposure, electrical, chemical), when the injury occurred, and what treatments have been used on the wound [4]. Law enforcement may be able to provide the physician with the temperature of the hot water that allegedly caused the burn (remembering that at 156° a child can sustain a third degree burn from hot water in 1 s) [5]. The appearance and location of the injury may help to confirm or disprove the history of injury mechanism that is provided. Also the absence of burn areas should be noted (clenched fist or curled toes in an immersion burn, sparing some area of fingers and toes) as it may suggest whether or not the injury was inflicted or accidental. Patterned burns should be noted. Burn age cannot be determined by examination. There is an association between inflicted burns and fractures [7].

The workup for burns should be the same as that for bruises including consideration of CT, MRI, and skeletal surveys in the evaluation of injuries.

Fractures

The differential diagnosis for a fracture includes medical conditions as well as accidental or non-accidental causes. The history of how the injury occurred is often unavailable, and the physical exam may be noncontributory, depending on the age and developmental maturity of the victim as it is not uncommon for a child, under the age of two who has fractures, to have no findings on exam (bruising, swelling, or deformity) [4, 8]. The history should include questions regarding a family history of metabolic bone disease [3].

The mechanics of the observed fracture must also be considered (spiral fractures suggest a rotational-type injury; a transverse fracture suggests a force perpendicular to the bone; corner metaphyseal fractures suggest shaking or rotational injury history) and the low mineralization of the bone of the infant can limit the usefulness of x-rays until healing begins [6]. Therefore, the provider must be aware of the limitations of radiographs in young children, and repeat radiographs in 2–3 weeks should be considered [5, 9]. Fractures concerning abuse include fractures in a nonmobile child, fractures of multiple ages/stages (of healing), and unusual fractures (sternal, vertebral). In addition, no history of injury or a history that is inconsistent with the injuries observed should raise the clinicians' suspicion.

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With the finding of multiple fractures, consideration of the presence of a metabolic bone disease might trigger laboratory testing or consultations with genetic or endocrine specialists.

The screening and laboratory testing should include phosphate, alkaline phosphatase, PTH, vitamin D, and calcium. Testing for osteogenesis imperfecta should be deferred unless family medical history, physical findings (easy bruising, hearing loss, growth deficiency, blue sclera), or genetics consultation suggests that it is indicated.

Radiographs should involve a skeletal survey or individual bone x-rays. The skeletal survey should include both the initial films and a repeat skeletal survey in 2–3 weeks. Repeat testing is done to look for healing fractures not identified on the initial films (due to the limited mineralization of an infant's bones), as well as to identify normal variants that initially appear to be a fracture but show no interval healing changes on the repeat films. The skeletal survey should follow the recommendations set by the American College of Radiology [5, 7, 9]. The testing should include individual x-rays of the upper and lower segments of the arms and legs and obliques of the chest to evaluate the ribs for posterior fractures, as well as complete views of the spine. Skeletal surveys are indicated for all children, under the age of 2, with physical abuse concerns. For the abuse victim over the age of 2, a good medical exam and specific bone x-rays (where deformity or tenderness is identified) can be ordered. If an adequate examination is not able to be completed, a skeletal survey for children between 2 and 5 years of age might be considered. Bone scans are rarely indicated due to the radiation dose involved. In addition, growth plate enhancement may potentially obscure corner metaphyseal fractures in bone scans. Radiographs should be reviewed with a radiologist regarding unusual healing patterns and possible normal variants. Due to variations in radiographic manifestations of healing, the ability to precisely date the age of fractures may be limited, but are improved with follow-up radiographs that assist in narrowing the window of time in which the fracture occurred.

Head Trauma

Findings of intracranial injury in an infant without an adequate history of injury must raise the question of non-accidental trauma. The diagnoses of inflicted head trauma or non-accidental head trauma may be used instead of reference to "shaking," as the physician may not know the exact mechanism of injury. The presence of a subdural hematoma (SDH), retinal hemorrhages, and a brain injury does not prove abusive head trauma. The physician must consider each of the injuries as well as other injuries and evidence in the evaluation. In addition, an assessment of medical conditions that might cause the clinical picture should be considered. The initial testing often begins with a non-contrasted CT of the head, as it may demonstrate intracranial bleeding [10]. Soft tissue swelling and fractures using CT bone windows can offer additional information. Further evaluation of the intracranial injury may require an MRI of the head and neck to discover more subtle injuries and to detect ligamentous injury suggesting acceleration/deceleration injury [11]. The purpose of the testing is to assist with both acute care and also to predict possible future potential medical problems. For example, a young infants' prognosis might be improved after injury by early intervention with resources such as physical and occupational therapy. If an MRI is performed, the test should be delayed for 1–3 days after the CT if possible in order to have a better opportunity to observe changes such as diffuse axonal injury [11, 12]. One cannot accurately determine the age of a SDH based on CT or MRI but they may provide an approximate window of time for the injury to have occurred within. The mechanics of abusive head trauma involve acceleration/deceleration as the cause for the tearing of bridging veins and the resulting SDH [13]. The findings of significant brain injury after a short fall (under 5 ft) or no history of injury, in an otherwise healthy infant or child, are very uncommon and suggest a non-accidental cause [10, 11, 13].

Evaluation should include lab testing to include coagulation profile; urine organic acid and serum amino acid testing; liver function testing; amylase, lipase, and UA testing [14], and testing to evaluate the

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abdomen for possible injury. Consultation with genetic specialists may be indicated as part of any evaluation for other causes of intracranial bleeding.

Retinal hemorrhages (RHs) may be observed in both accidental and non-accidental trauma. A complete dilated eye exam should include the presence and location of the RH and the presence of other findings such as retinoschisis. Photodocumentation should be obtained of any hemorrhages if possible. Other causes of RH, including genetic or infectious conditions, should be considered and ruled out. An examination by an ophthalmologist should be completed within 72 h of hospital admission [15, 16].

Sexual Abuse

One in six males will experience sexual abuse and as many as three out of six females. Disabled children are 1.7 times more likely than other children to be the victims of sexual abuse [1]. A physician should become familiar with the laws of the jurisdiction in which they practice (age of consent and ability to seek STI evaluation or contraception without parental consent). Sexual abuse not only involves acts of penetration but also includes voyeurism, exhibitionism, and pornography (being exposed to pornography or being photographed). Trafficking involves the use of a child in prostitution. This has become a significant national problem in the United States [17].

Screening for possible abuse should involve a complete history and a forensic interview. It is important to remember that younger children will provide a history that may be very concrete, so that "touching" can refer to abuse, but also may refer to wiping the genital area after urination or a bowel movement, the application of medication, and so on. For this reason the forensic interview is best conducted by someone specifically trained in interviewing children. When collecting a history from the caregivers, it is important to ask about any known or possible exposure to sexual material in the child's environment (video, television, etc.).

Disclosures of sexual abuse are most often delayed, sometimes by many years. The offender often works to maintain a relationship with the child, in order to ensure the child's silence about sexual acts. Although a child's disclosure may be made piecemeal, the physician should document the information. Disclosures given during the medical interview may be admitted to court as hearsay evidence and may be the only evidence available.

The history should be as complete as possible, including both acute events and past medical history to document any exam findings that might be related to medical causes or previous accidental injuries. Up to 95 % of exams will be normal by the time the child/teen is examined (due to healing, pubertal changes, and so on) [18]. It is important to remember that a "normal exam" does not rule out prior sexual abuse or penetration. Most often normal findings can be reported in the physicians' note as "consistent with the disclosure." The disclosures given during the visit should be recorded verbatim in the medical record, with the use of quotation marks to signify this ("grandpa touched me here"). When evaluating possible reports of abuse, an evaluation for normal childhood behavior (exploratory between children of similar ages and imitation of observed sexual acts on TV or other media) should be done. The physician should also have a guideline for determining the urgency of an examination. The guidelines may be mandated by local jurisdictional requirements. For example, immediate evaluation should be carried out after a reported or suspected sexual act has occurred within the last 72 h in a prepubertal child, the presence of any reported bleeding or purulent drainage, suicide risk, or suspicion of the child being in an unsafe environment.

The physical examination for a child who may have been a victim of sexual abuse [19, 20] should include Tanner staging, a complete head to toe exam, and a colposcopic evaluation of the anogenital area, if this is available. A speculum exam is not usually indicated unless there is bleeding or purulent drainage,

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in which case evaluation (for the prepubertal child) should be carried out under moderate sedation. The exam should evaluate the entire anogenital area, noting bruising, abrasions, lacerations, etc. An examination with a specialized ultraviolet light source (not a Wood's lamp which is not sufficiently specific to detect the presence of semen) should be done at the beginning of the exam, for identification of areas to collect specimens for the forensic kit [21]. The physician should be familiar with the required components of the forensic sexual assault kit, since these differ depending on legal requirements. The term "intact hymen" is an obsolete term and should not be used in the exam or impression. The examiner must have the experience and skills to know the difference between changes due to trauma and those due to normal variants or medical conditions. Any findings, consistent with injury (to the anogenital areas), should be reexamined in follow-up, at 2–4 weeks, to show resolution of the injury (and to rule out a medical condition that might mimic an injury).

The anal exam should include a visual inspection and colposcopic exam. Looking at the tone of the sphincter and perianal area for changes (flattening of the rugae, abrasions, fissures, bruising) is important. The physician must be familiar with normal variations including venous stasis, funneling, and diastasis changes as well as being aware of the rapid healing that occurs in this area.

Laboratory testing for pregnancy, sexually transmitted diseases and updating tetanus vaccine, as well as providing any wound care, should be considered for each victim. Some testing may need to be repeated in the future, such as HIV, RPR, or hepatitis B or C. The physician must determine whether prophylaxis is indicated for pregnancy and STIs such as HIV, hepatitis, or others.

Medical Child Abuse

Previously, this type of abuse was called Munchausen by proxy. This form of abuse involves excessive use of medical care (and/or ancillary services) at the request of the caregiver that may have harmful effects on the child [22]. This may include demands of the parent for surgical procedures, multiple specialty consultations, or hospitalizations for symptoms attributed to the child by the caregiver. The actual incidence is unknown as the identification and prosecution of this type of maltreatment can often be very difficult to demonstrate or identify. Key points in making the diagnosis include a comprehensive review of all records and tests and discussion with previous health care providers regarding the diagnosis and any suspicions of involvement by the caretaker in producing symptoms or unusual behavior [23]. Looking for patterns that might include excessive or missing medical visits, unusual and recalcitrant unexplained symptoms, and unexplained deaths in family members or siblings may also raise red flags for this condition.

Neglect

Neglect differs from child maltreatment as it involves an omission of care, rather than an act of commission. With neglect, the needs of the child are not being provided for. As with abuse in general, the age group under 3 is at greatest risk. It is important to remember that during the first 3–4 years of life, much of a child's emotional development, nutrition/growth, and skill development are occurring. Neglect may result in the window of development being missed. This results in long-term medical and mental health consequences [23]. There are many types of neglect including educational, supervision, clothing, housing, dental, and others. The physician often becomes involved for concerns involving growth, including obesity and failure to thrive, and medical neglect [30]. Having an understanding of the barriers that the caregiver is experiencing is needed before success at reunification and safety for the child may be achieved. Referral does not always result in the removal of the child or prosecution of the caregivers. The physician must remember that reporting neglect can often be very beneficial to a family which is struggling, as services can be brought into place to assist them.

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Failure to thrive is a clinical diagnosis and the workup should include both organic and nonorganic causes. The workup of this condition should include bringing together all of the previous records of the child from birth to present (including the nursing notes), for review. History obtained from the caregiver should be detailed and include family medical history, past medical history, diet history, and social, cultural concerns and development. In addition, the caregivers' impressions of the child's growth and development should be sought. A review of all growth parameters should be completed, and any changes in the slope of the growth curves can be analyzed. Hospital evaluation is not often indicated for the evaluation, but should be considered in severe cases.

Laboratory testing should be considered both to exclude organic causes of FTT and to more completely assess any associated conditions, such as iron deficiency anemia, which may arise as a result of poor nutrition [24, 25]. These should be determined on a case-by-case basis. Likewise, consultations may be indicated, and often evaluation, and subsequent care, requires a multidisciplinary team that may include nutritionists, public health workers, subspecialty pediatric providers, social services, and extended family.

Obesity has become a major health concern in the United States, with up to 30 % of the pediatric population having significant weight problems, putting them at risk for medical complications. Obesity can be caused by neglect [26]. Initial steps include interventions for both child and caregiver, consideration of dietary consultation, public health involvement, lab testing, and close follow-up. If the child has complications from the obesity, particularly if they are potentially life threatening, the physician should file an abuse and neglect report promptly.

Medical neglect [6, 27] occurs when the caregiver chooses to not follow instructions or provide medical care for a child that either has the potential to have a negative health impact or has caused actual harm to the child. The care recommended must (1) be available and (2) have greater benefit than risk. An example would be the need for ongoing laboratory testing for a child on a chemotherapeutic drug that might have harmful liver or bone marrow effects and the parent refuses to allow testing.

Barriers to obtaining care must be identified and assistance may be sought from multiple agencies. Clearly outlining the care plan and the expectations of the outcome of treatment, as well as the reasons for the testing or medications, and then documenting in the clinic notes that the caregivers "understand and agree to the care plan" provide documentation for the providers to work for should the caregivers fail to follow through with the plan of care.

Prevention

Reducing the risk of abuse and neglect can be part of the physicians' practice in a number of ways. First, and most important, the physician should maintain a holistic view of the patient and family in day-to-day clinical practice, observing and being aware of the early family dynamics and stresses that may lead to child abuse. It is important to help the caregivers recognize that it is okay to be frustrated, but having a healthy method of dealing with the frustration or having the ability to contact the physicians' clinic to discuss options is the correct way to deal with it. Second, becoming involved in training projects such as the Period of PURPLE Crying [28], to help reduce the non-accidental head injuries or to be willing to provide community education and support on areas of child abuse and neglect, will raise the consciousness of the entire community. It is also important for physicians to continue to update their knowledge on this subject through education and training.

Summary

Child abuse and neglect are an everyday part of primary care practice. The physician must recognize and be able to respond to the abuse or neglect in a timely manner, in order to ensure the safety of the child. Consider consultation or curbsides with a child abuse expert early on in the course of care, since you must

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be able to explain your evaluation and treatment in court. Also become familiar with the resources available in your region (Children's Advocacy Center, Child Abuse Pediatrics experts).

The effects of child abuse can reverberate across the lifetime of the patient. The physician must continue to monitor and anticipate the possibility of problems in adolescence and adulthood because of previous exposure to abuse. Mental health services, by a mental health provider trained in trauma-focused therapy, are critical in helping both the family and the victim move forward and perhaps to have healthy relationships in the future.

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Intimate Partner Violence

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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 five major subtypes of IPV:

1. Physical violence
2. Sexual violence
3. Stalking
4. Psychological aggression
5. Control of reproductive or sexual health

According to this study, 35.6 % or approximately 42.4 million American women have experienced physical violence, sexual violence, or stalking at some point in their lifetime. Among men, lifetime prevalence is 28.5 % [1]. While the vast majority of male victims experienced only 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]. Additionally, about half 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

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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 as well as 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 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 starts to spin 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, hairpulling, hitting, and being beaten, restrained, burned or choked, or harmed 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, or forced participation in unwanted sexual experiences. Nearly one out of ten American women reports being raped by an intimate partner in her lifetime, and one in six has experienced another form of sexual violence by an intimate partner. 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, 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 5 % 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

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killed. While stalking can be perpetrated by a stranger, two thirds of female victims report being stalked by a current or former intimate partner [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, 48 % 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 convincing them to stay.

Control of Reproductive or Sexual Health

An IPV perpetrator may undermine his partner's ability to control her reproductive choices in order to maintain a position of power in the relationship. Forced sex, unwillingness to use contraception, and interference with access to reproductive health services have been documented in many relationships that include IPV. Thus, IPV is associated with unwanted pregnancy, sexually transmitted infections, miscarriages, repeat abortions, and poor pregnancy outcomes [4].

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 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. Individuals who suffer from IPV are more likely to have sexually transmitted infections (STIs), pelvic inflammatory disease, and unintended pregnancies. 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 post-traumatic 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

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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].

In 2007, 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 the police or medical or mental health officials. Female victims of murder had 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 one intimate partner murders the other and the children and then kills him- or herself. 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].

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 transwomen are not welcome and even fewer shelters that can assist male victims.

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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 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 non-abused 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 stimulate early labor and restrict uteroplacental perfusion [15].

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 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 [16]. 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 apply the same violent patterns they have learned at home in these relationships [17].

Teens

Teen dating violence is a widespread issue with 9 % of high school students reporting being hit, slapped, or physically hurt by a boyfriend or girlfriend in the past year [18]. 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.

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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. 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 [19]. 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 [20]. 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 [21].

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 [22]. 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 well equipped to manage their medical as well as social needs. 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 [23].

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 [24]. 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.

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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. Updated to 2003 dollars, costs would total over $8.3 billion [25].

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 [26]. 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 [27].

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 [27].

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 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.

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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) [28]

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 also interesting 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 [29]. 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 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.

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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 her/his 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.

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

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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 non-accidental 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, health-care 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 [30].

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Sexual Assault

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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 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].

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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. 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

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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 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

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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

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

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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 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

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policies and procedures, campus and community safety programs, and 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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Family Stress and Counseling

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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. However, stress is often difficult to define and study, in relation to both physical symptoms and external causes [2]. 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 [3]. 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 [4, 5]. 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 [6]. 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 [7, 8]. Greater health risks and the incidence of suicide also increase as a result of divorce [9]. Childhood adjustment can be affected greatly by parental divorce; it is reported that 25 % of children from these families experience high levels of problem behaviors [10]. 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 [11].

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 [12] or asthma [13]. 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 [14]. 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 [15]. 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).

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

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 stress. According to the National Alliance of Caregiving [16], 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

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 [17]. Bowen [18] 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 [19].

McDaniel et al. [20] highlighted the following concepts and questions to help physicians apply systems theory into practice with families:

- **The Family as a System**
  - Who are the members of the patient's family?
  - When it comes to daily support, who does the patient consider as family?
- **Family Stability**
  - 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**
  - 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**
  - How do the patient's symptoms influence the family?
  - How does the family influence the patient's symptoms?

Mind-Body-Environment

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 [21]. Antonovsky believed that health, stress, and coping are interrelated factors, and professionals should not focus solely on the factors that cause disease [22]. George Engel [23] 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 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 [24]. 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

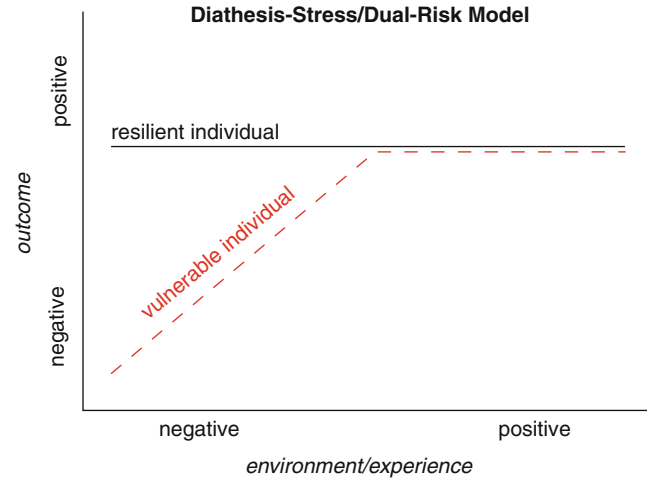

Fig. 1 Diathesis-stress model

"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.

Developmental and Multigenerational

Families often lack a clear perspective of time when problems or crises occur. Members may be 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 [25], 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 [26]. 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 [27].

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. 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.

Crisis and Adaptation

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

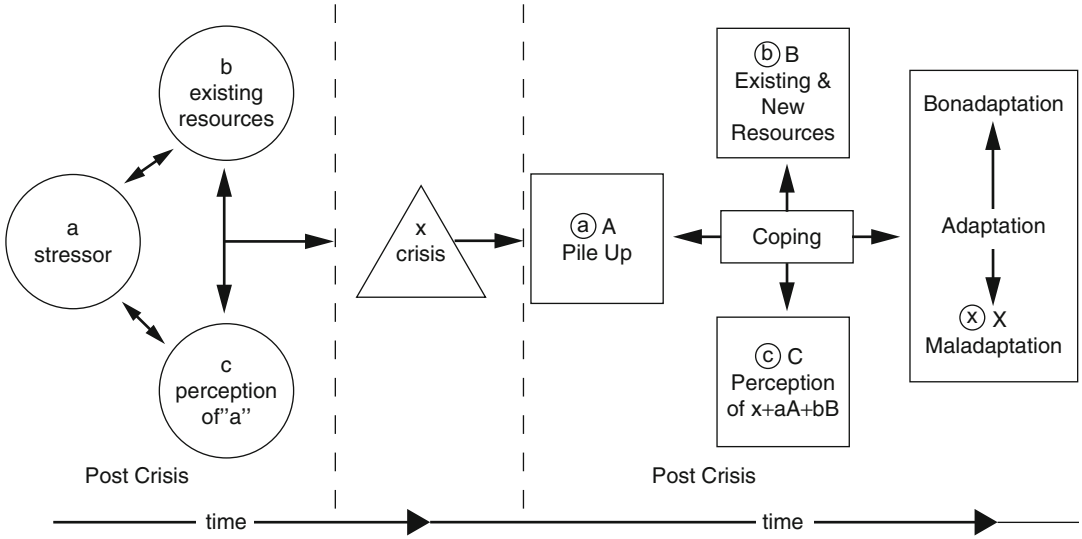

Fig. 2 The double ABCX model [29]

crisis model [28]. 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 [29] expanded this model, including a second level of coping and adaptation after a stressor (Fig. 2).

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). These systems work together to send signals to all areas of the body to prepare for the possibility of fight or flight [30]. 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 [31].

Acute Stress

The entire body is affected by heightened hormonal and nervous system responses to an acute stressful event. The initial response begins with the nervous system and hormonal response. 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 [31]. 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.

As the acute stress continues, muscle tension increases as blood supply is diverted to prepare the body for action. 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 [33].

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. 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. These results are observed in stress-related bowel disorders [34]. Lastly in the acute stress state, the reproductive organs are affected. There is decreased blood supply to the genitals [33]. 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 [35].

Chronic stress may have negative effects at any age. A recent study of post-hip fracture geriatric patients found that those with depression as a marker of chronic stress demonstrated reduced bactericidal functioning of monocytes [36]. 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 [37]. 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 brain. Tension headaches, backache, shoulder

Table 2 The effects of stress

System	Acute stress effect	Chronic stress effect	Diseases worsened
Mood and memory	Increased anxiety	Panic attacks	Anxiety
	Decreased short-term memory	Memory problems	Depression
Musculoskeletal system	Tension	Pain	Tension headaches
			Chronic pain
Respiratory	Tachypnea	Shortness of breath	Asthma and COPD exacerbation
Cardiovascular	Elevated blood pressure	Hypertension	Hypertension
	Tachycardia		CAD
			ACS
Endocrine	Elevated hormones	Hyperglycemia	Diabetes
	Elevated blood glucose		
Gastrointestinal	Constipation	GERD	Irritable bowel syndrome
	Diarrhea		Inflammatory bowel disease flares
	Increased gastric acid		
Sexual and reproduction	Male erectile dysfunction	Decreased libido	ED
	Female menstrual changes		PMS
			Menopause

pain, and chronic pain syndromes can all develop from chronically tense muscles [32].

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 [34].

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 [31]. 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. There is an increased risk of developing type 2 diabetes.

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 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 [38]. The coronary arteries are also very sensitive to the stress hormones released during the acute response [33]. 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 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 sections will highlight these approaches when working directly with the patient as well as the family system.

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 [39]. As a patient-centered method for enhancing motivation to explore change and challenging ambivalence, MI has expanded to also elicit and strengthen change for individuals around illness [40]. 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 [39]:

- 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.

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 [41]. SFBT has been implemented in family services around mental health and family-related issues, public social services, prisons, residential treatment centers, schools, and hospitals [42]. Behavioral health professionals and other providers who use this framework 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 [43].

Healthcare professionals using 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 [44–46] but for self-regulation and stress reduction around mental health and family-related stress [47, 48]. 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 [49].

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

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 [50]. 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.

Healthcare professionals using mindfulness should implement the following key steps [51]:

- *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 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 [52] 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 [53].

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 members have been unable to cope with life events. Bowen's theory [26] 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.

Specific processes that physicians can attend to by using this approach 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.

Collaborative/Integrative Care

The family physician is situated in a system of care that, when used, can greatly facilitate the amelioration 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 [54].

In the area of coping with family stress, one resource that helps patients and families work through crisis and illness situations is a medical family therapist. The field of medical family therapy has gained increasing prominence in helping to address the psychosocial aspects of illness in individuals and families. Approaching primary care from both the biopsychosocial and systemic perspective, medical family therapists are trained to intervene with individuals and families to address both mental disorders and interpersonal

dysfunction. As part of the collaborative care team, medical family therapists can provide support services ranging from behavioral consultations to short-term interventions to intensive individual and family psychotherapy [55].

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Managing Mentally Ill Patients in Primary Care

Laeth Nasir

Contents

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 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

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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 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 is 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.

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 "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 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, petichiae, 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 acknowledgement 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 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 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 allows for patient and family self-regulation.

Prevention

Mental illness, like many physical illnesses have 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, should be specifically explored by the physician with the patient. These sources of 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, is 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. The anxiety disorders listed in the DSM-5 tend to be highly comorbid with other psychiatric conditions [1]. The DSM-5 chapter on Anxiety Disorders no longer includes obsessive-compulsive disorders, post-traumatic stress disorder, or acute stress disorder, which had been included in this section in the DSM-IV/DSM-IV-TR. Due to their relevance, these associated disorders will be discussed briefly in this chapter. Relevant changes to anxiety disorders in the DSM-5 are outlined in Table 1. Of note, 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. Panic disorder and agoraphobia have been unlinked in the DSM-5, and panic attacks can now be listed as a specifier, applicable to all DSM-5 disorders [1]. 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 and/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, 25].

Separation Anxiety Disorder

Separation anxiety disorder is categorized by excessive and developmentally inappropriate fear or anxiety triggered by separation from home or attachment figures. There is persistent fear or anxiety of potential harm toward the attachment figure and/or worry about events that could lead to loss of or separation from attachment figures. 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.

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Table 1 Summary of DSM-V Anxiety Differential by age of onset

Disorder	Age at onset	DSM-5 changes
Separation anxiety disorder	Preschool–adolescence	Newly classified DSM-5
Selective mutism	Less than 5 years	Newly classified DSM-5
Reactive attachment disorder	9 months–5 years	Reclassified under Trauma- and Stressor-Related Disorders
Disinhibited social engagement disorder	2 years–adolescence	Reclassified under Trauma- and Stressor-Related Disorders
Specific phobia	Early childhood < age 10 years	Anxiety no longer is seen as "unreasonable"; now "out of proportion to danger or threat"
Social anxiety disorder (social phobia)	Adolescence	"Generalized" specifier deleted and replaced with "performance only" specifier
Panic disorder	Early adulthood	Panic disorder and agoraphobia unlinked in DSM-5
Agoraphobia	Early adulthood	Panic disorder and agoraphobia unlinked in DSM-5
Generalized anxiety disorder	Early adulthood	No change
Substance-/medication-induced anxiety disorder	Variable	Diagnoses merged in DSM-5
Anxiety disorder due to another medical cause	Variable	No change
Other specified anxiety disorders	Variable	Merged from "NOS" DSM-IV-TR
Unspecified anxiety disorder	Variable	Merged from "NOS" DSM-IV-TR
Obsessive-compulsive and related disorders	Late adolescence–early adulthood	New classification; includes new disorders
Post-traumatic stress disorder	Early childhood–adulthood	Reclassified under Trauma- and Stressor-Related Disorders
Acute stress disorder	Early childhood–adulthood	Reclassified under Trauma- and Stressor-Related Disorders
Adjustment disorders	Early childhood–adulthood	Reclassified under Trauma- and Stressor-Related Disorders

The onset of separation anxiety disorder can start as early as preschool, but is more commonly diagnosed during childhood and less commonly in adolescence. The disturbance must last for at least 4 weeks in children and 6 months in late adolescence. Individuals may exhibit sadness, social withdrawal, and a 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, PTSD, social anxiety disorder, agoraphobia, OCD, and personality disorders [1].

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. Occasionally, a diagnosis of selective mutism may be delayed until a child enters school and more attention is placed on social interactions. 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 and/or intellectual

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disabilities should be considered in the differential diagnosis. Social anxiety disorder is a common comorbidity and should be identified and treated if present [1, 4].

Reactive Attachment Disorder

Reactive attachment disorder is classified under Trauma- and Stressor-Related Disorders in DSM-5 [1]. It typically presents between the ages of 9 months and 5 years and is characterized by noticeably inappropriate or disturbed attachment behaviors. The affected child rarely or minimally turns preferentially to an attachment figure for comfort, support, or nurturance. There is an absence of expected comfort seeking and response to comforting behaviors. A paucity of positive emotions during routine interactions with caregivers is a frequent observation. This disorder is commonly comorbid with social neglect and developmental delay [1].

Disinhibited Social Engagement Disorder

Also classified under Trauma- and Stressor-Related Disorders in DSM-5, disinhibited social engagement disorder presents in children between the ages of 2 years and adolescence. This disorder encompasses a pattern of behavior that involves culturally inappropriate or overly familiar behavior with strangers, violates cultural and social boundaries, and is associated with a history of serious social neglect. Comorbid conditions include cognitive delays, language delays, and attention-deficit hyperactivity disorder (ADHD) [1].

Specific Phobias

Specific phobias involve the manifestation of marked fear, anxiety, or avoidance in the context of specific objects or situations. Individuals with specific phobias commonly have fears of more than one situation or object. Specific phobias may develop after a traumatic event; however, the trigger is not always identifiable. There are various types of specific phobias: objects, animals, natural events, and situational. Symptoms usually develop in early childhood, predominantly before age of 10 years, and usually fluctuate in occurrence. Symptoms which persist into adulthood tend to be persistent and are unlikely to remit. Specific phobia, though low in prevalence, remains a commonly experienced disorder in late life [1].

Social Anxiety Disorder (Social Phobia)

Social anxiety disorder (social phobia) is characterized by marked fear, anxiety, or avoidance of social situations where possible scrutiny by others may occur. Examples may include meeting new people, eating in public restaurants, and speaking or performing in public. The specifier of "performance only" was added in the DSM-5 to denote fear that is restricted to speaking or performing in public. The average age of onset for social anxiety in the United States is 13 years. This disorder is associated with an elevated school dropout rate. Lack of employment is a strong predictor for social anxiety disorder. Depression is a common comorbidity in social anxiety disorder, as well as the use of substances to help mitigate social fears [1].

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Panic Disorder

Panic disorder is characterized by recurrent unexpected panic attacks, which may result in behavior changes related to the attacks or persistent concern about subsequent panic attacks. Panic attacks are described as intense surges of fear and discomfort that peak quickly and then dissipate. Symptoms of a panic attack include four or more of the following: palpitations, diaphoresis, trembling, shortness of breath, choking sensation, chest pain, nausea/abdominal discomfort, lightheadedness, heat/cold intolerance, paresthesias, derealization or depersonalization, fear of losing control, and fear of dying. The attacks can be expected, in response to a typical trigger, or be completely unexpected. The median age of onset in the United States is 20–24 years. 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 individuals who are fearful and/or anxious 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. The onset of agoraphobia is typically early adulthood. The situational fear encompasses thoughts of inability to escape or of becoming embarrassed. The course is typically persistent and chronic, with only 10 % remission reported. Approximately a third of affected adults are homebound and unable to work. Common comorbidities include other anxiety disorders, depressive disorders, post-traumatic stress disorder (PTSD), and alcohol use disorder [1].

Generalized Anxiety Disorder

Generalized anxiety disorder (GAD) is characterized by excessive and persistent worry that is difficult to control, causes significant distress and/or impairment, and occurs most days for at least 6 months. GAD is twice as common in women as it is in men and is the most common anxiety disorder among the elderly population [5, 6]. The typical age of onset is early adulthood. Symptoms include restlessness, feeling on edge, fatigue, poor concentration, irritability, muscle tension, and insomnia. GAD is typically comorbid with substance abuse, PTSD, and obsessive-compulsive disorder (OCD). Major depressive disorder that is comorbid with GAD portends a more severe and prolonged course of illness and a greater functional impairment [22]. GAD is also common among patients with chronic pain and with unexplained chronic physical illness [1, 3].

Other Anxiety Disorders

This group of disorders includes the following: substance-/medication-induced anxiety disorder, anxiety disorder due to another medical cause, other specified anxiety disorders, and unspecified anxiety disorder. Substance-/medication-induced anxiety disorder presents with symptoms of panic and anxiety that have developed during or immediately following intoxication and/or withdrawal of a substance or medication. Anxiety disorder due to another medical condition is explained by the physiological effect of an underlying medical condition (e.g., hyperthyroidism, arrhythmia, asthma, seizure disorders).

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Other specified anxiety disorders and unspecified anxiety disorders do not fit criteria for one of the aforementioned anxiety disorders [1].

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-/medication-induced OCD, OCD due to another medical condition, and unspecified OCD. 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 that result (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, 7].

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 attempts to cease. These two disorders are usually preceded by feelings of anxiety or boredom [1, 7, 8].

Substance-/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 [9].

Post-traumatic Stress Disorder (PTSD)

PTSD is listed under the category of Trauma- and Stressor-Related Disorders in the DSM-5. 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. Symptoms of PTSD vary in clinical presentations and may involve dysfunction in five domains: intrusive thoughts, mood changes, dissociative reactions, avoidance, and marked alterations in arousal. 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. Symptoms can begin within 3 months after exposure to a traumatic event; however, symptoms can also present much later before criteria for a full diagnosis of PTSD are met. Acute stress disorder and adjustment disorder are classified similarly but fall short of meeting all requirements for PTSD [1].

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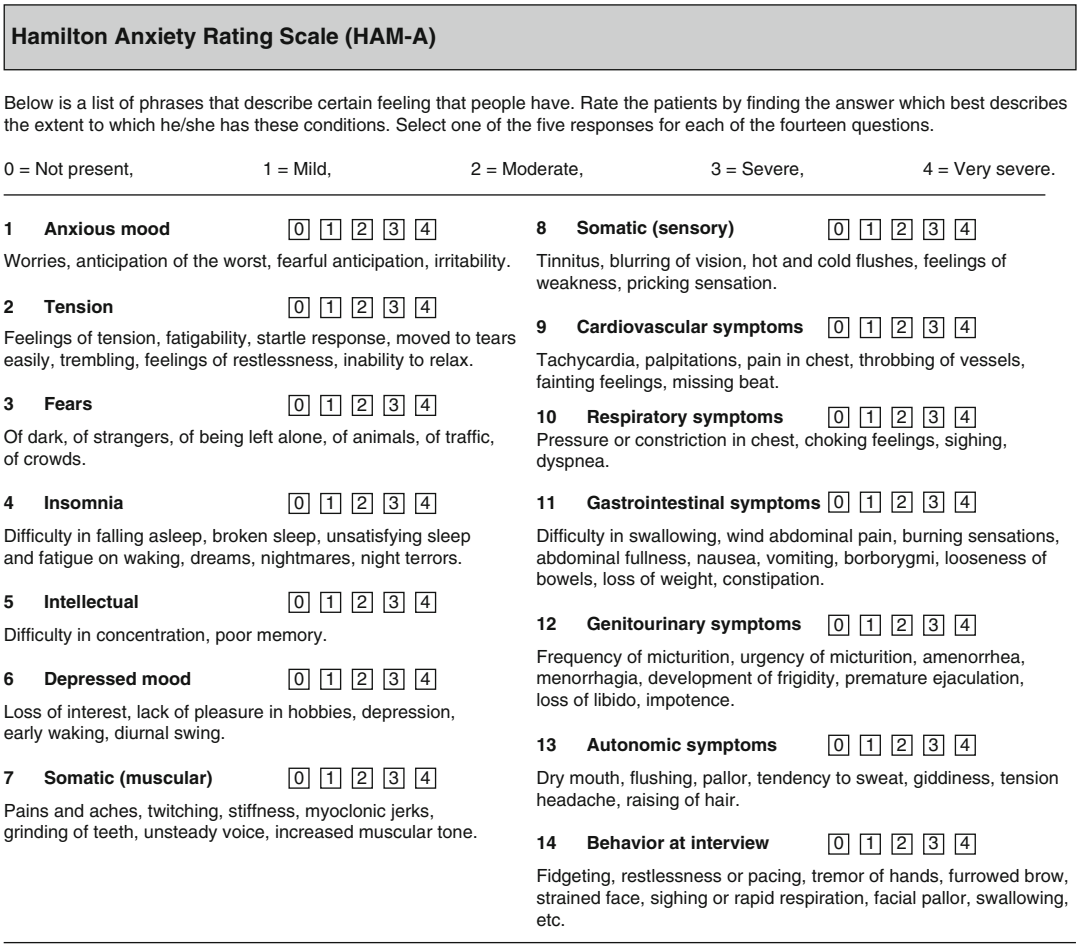

Hamilton Anxiety Rating Scale (HAM-A)

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
Worries, anticipation of the worst, fearful anticipation, irritability.

2 Tension 0 1 2 3 4
Feelings of tension, fatigability, startle response, moved to tears easily, trembling, feelings of restlessness, inability to relax.

3 Fears 0 1 2 3 4
Of dark, of strangers, of being left alone, of animals, of traffic, of crowds.

4 Insomnia 0 1 2 3 4
Difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors.

5 Intellectual 0 1 2 3 4
Difficulty in concentration, poor memory.

6 Depressed mood 0 1 2 3 4
Loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing.

7 Somatic (muscular) 0 1 2 3 4
Pains and aches, twitching, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone.

8 Somatic (sensory) 0 1 2 3 4
Tinnitus, blurring of vision, hot and cold flushes, feelings of weakness, pricking sensation.

9 Cardiovascular symptoms 0 1 2 3 4
Tachycardia, palpitations, pain in chest, throbbing of vessels, fainting feelings, missing beat.

10 Respiratory symptoms 0 1 2 3 4
Pressure or constriction in chest, choking feelings, sighing, dyspnea.

11 Gastrointestinal symptoms 0 1 2 3 4
Difficulty in swallowing, wind abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation.

12 Genitourinary symptoms 0 1 2 3 4
Frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of frigidity, premature ejaculation, loss of libido, impotence.

13 Autonomic symptoms 0 1 2 3 4
Dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair.

14 Behavior at interview 0 1 2 3 4
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)

Screening Tools for Anxiety Disorders

The Hamilton Anxiety Rating Scale (HAM-A), Fig. 1, was one of the first rating scales to measure severity of anxiety symptoms. It is widely used today in clinical and research settings. The 14 included items measure psychic and somatic anxiety. Each item is scored 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 [10]. It has been criticized, however, for its indiscriminate view of anxiety and depressive symptoms and their lack of congruency with the DSM-IV-TR and DSM-5 [11].

The Generalized Anxiety Disorder 7-item scale (GAD-7), Fig. 2, is an efficient screen that is utilized in primary-care clinics for screening and tracking anxiety disorder treatment and progress. It has been identified as a useful tool with strong validity for identification of probable causes of generalized anxiety disorder [12].

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 a combined model of pharmacotherapy and psychological

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Generalized Anxiety Disorder 7-item (GAD-7) scale

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

therapy [7, 13]. Achieving true remission is rare in these disorders. Goal-directed therapy should be emphasized and the use of combination therapy optimized to reduce individual morbidity and mortality [13]. 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 [7, 13]. A few of the antidepressants listed may be more activating than others (i.e., fluoxetine, sertraline, SNRIs) [14, 15]. The recommendation for pharmacotherapy is to start at the lowest dose possible and titrate up or increase slowly to minimize side effects and determine the lowest effective dose [15]. If discontinuation is needed, tapering is recommended to reduce withdrawal side effects.

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 data is lacking, these agents have not demonstrated harm. 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, with the exception of a small increase in headaches, and moderately effective for GAD [16].

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Table 2 First-line treatment of anxiety and related disorders

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. Fluoxetine (Prozac) 2. Paroxetine (Paxil) 3. 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

(*continued*)

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Table 2 (continued)

Diagnosis	Treatment(s)	Comments
Trichotillomania	SSRI 1. Fluoxetine (Prozac) Antipsychotics 1. Aripiprazole (Abilify) 2. Quetiapine (Seroquel) 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[d]	

[a]Ages 7–17 years
[b]Ages 8–17 years
[c]*CBT* cognitive 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 [7, 8, 9, 13, 15, 16, 23, 24, 25, 26]

Complementary and Alternative Methods

Yoga

Modern yoga is defined as "a systematic practice and implementation of mind and body in the living process of human beings to keep harmony within self, within society, and with nature." [17] Yoga is most well known to the Western world for its characteristic poses. Though there are many different ways that yoga may be practiced, common to all traditional schools of yoga are a regimen of poses, breathing techniques, and meditation.

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 [17]. This systematic review did not address any particular anxiety disorder diagnosis.

Exercise

Aerobic exercise provides psychological benefits of self-mastery, goal attainment, and socialization. Positive attributes of physical exertion include anxiolytic effects and resistance to both physiological and emotional consequences of psychological stressors. Data-supporting psychological benefits of

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physical exercise have historically been observational. Cross-sectional and longitudinal studies demonstrated the strongest support for use in mild to moderate anxiety disorders. Data were lacking for efficacy in panic disorder [18].

Acupuncture

Acupuncture is one of many practices used in traditional Chinese medicine that has been embraced by Western culture for the treatment of a variety of conditions. In the practice of acupuncture, thin needles are inserted into specific points on the skin to produce their therapeutic effect. In traditional practice, stimulating these points alters the flow of "Qi" or "life energy" which, in turn, alters the function of the entire human organism.

Though many studies have demonstrated the beneficial effect of acupuncture in treatment of anxiety disorders, high-quality evidence is still lacking. Common concerns raised in reviews are location of acupuncture points used, type of acupuncture used, duration of treatments, frequency of treatments, and adequate control groups [19].

Mindfulness

Mindfulness is perhaps one of the most studied interventions for stress and anxiety. Mindfulness, rooted in Buddhist teachings, is described as a cultivation of the practice of moment-to-moment awareness and observation of thoughts and feelings with an attitude of acceptance [20]. This can be practiced in daily situations such as driving a car or washing dishes, while more formal practice is typically termed meditation. Mindfulness practices also share common elements with cognitive behavior therapy (CBT).

In a literature review of 17 articles published from 2009 to 2014, mindfulness-based stress reduction techniques were found to have a positive effect on indicators of stress in otherwise healthy individuals [20]. A recent small study on the self-reported informal practice of mindfulness techniques correlated with lower anxiety severity, worry, and improved quality of life [21].

Summary

Anxiety disorders, obsessive-compulsive and related disorders, and trauma- and stressor-related disorders account for significant morbidity and mortality among mental health patients. Specifically, the anxiety disorders 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 combination therapy: CBT or exposure therapy coupled with first-line pharmacotherapy. Alternative herbal therapies lack significant efficacy data, but are considered safe for use and may be considered. 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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Depressive and Bipolar Disorders

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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 and 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 non-psychiatrists, such as family physicians, often

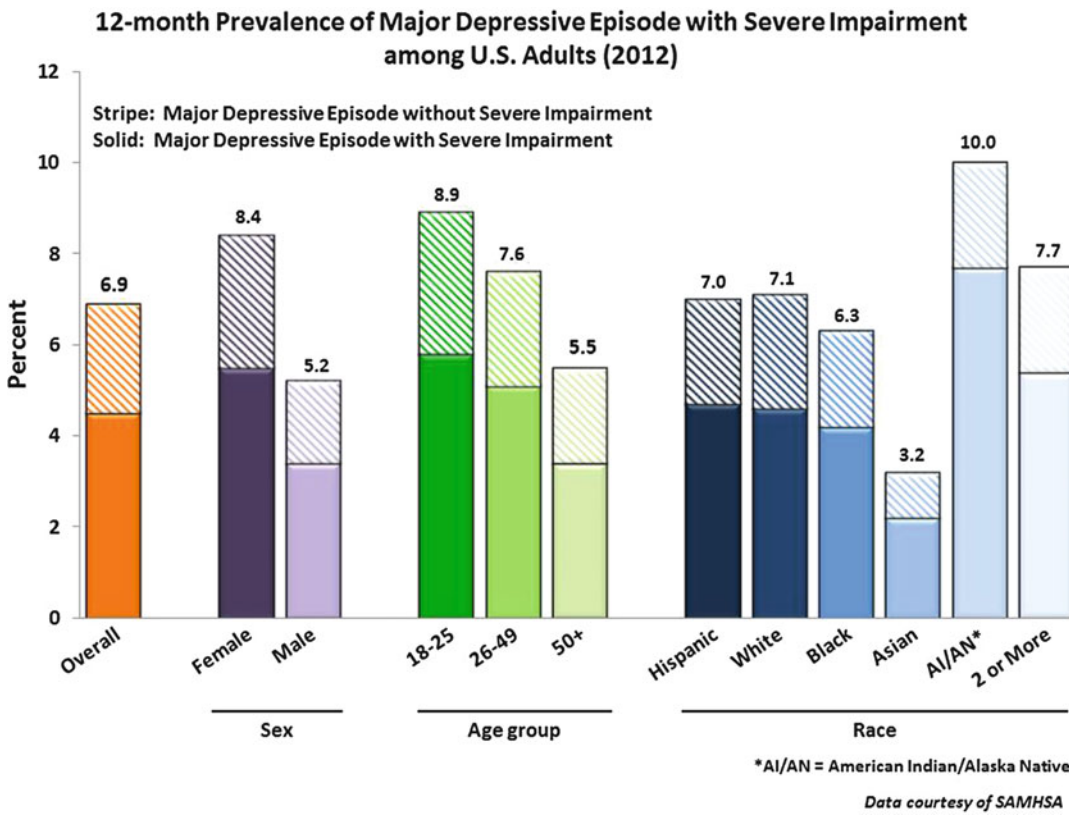


Fig. 1 National Institutes of Health 2012. Results from the 2012 National Survey on Drug Use and Health: http://www.nimh.nih.gov/health/statistics/prevalence/major-depression-with-severe-impairment-among-adults.shtml

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 non-depressed 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.

Diagnostic Criteria

Depressive Disorders

The *Diagnostic and Statistical Manual* of the American Psychiatric Association Fifth Edition (DSM5) now 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 DSM5 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 DSM5. 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 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."

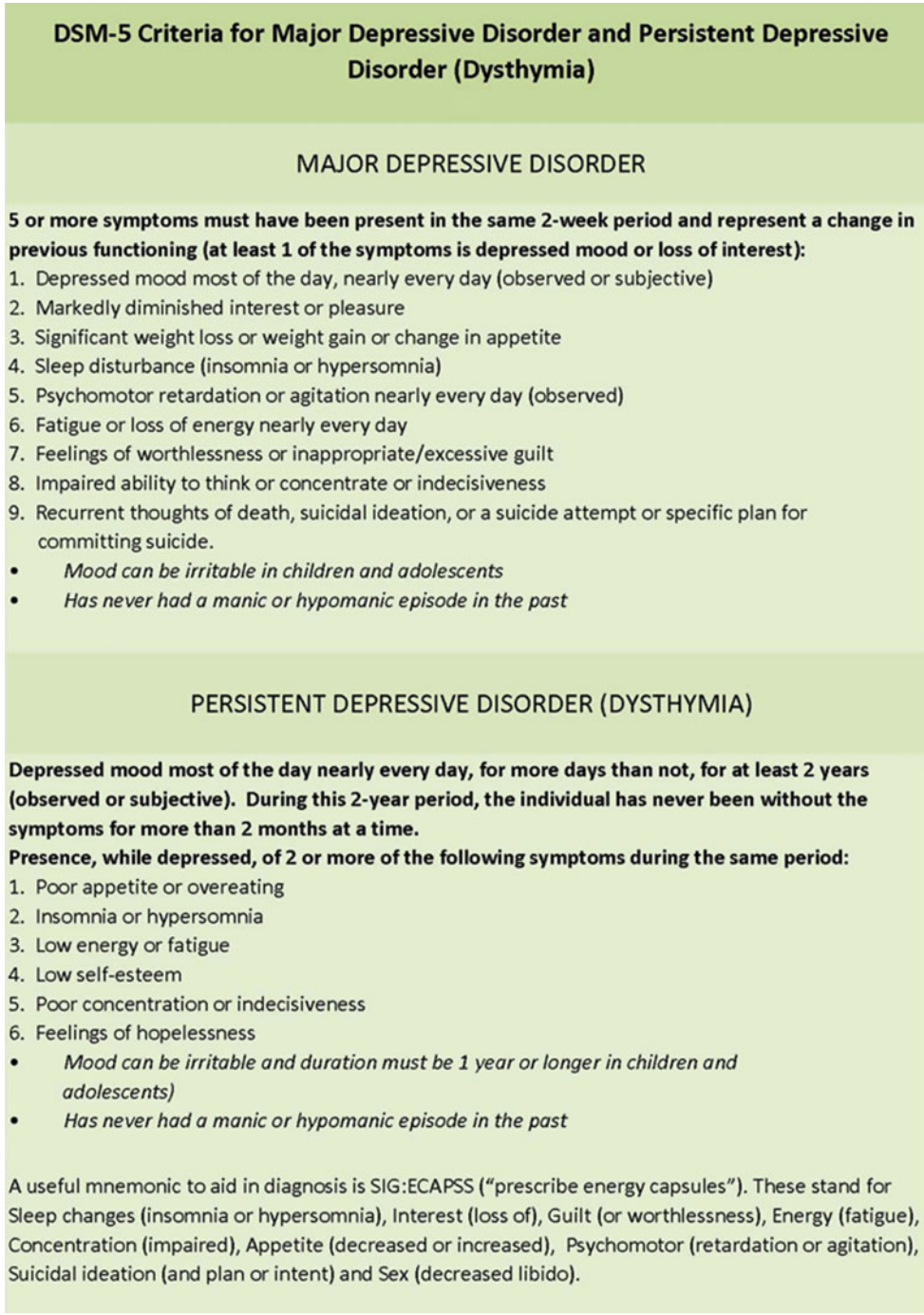
In primary care, a large number of patients present with somatic, rather than mood, symptoms. It is important that the family physician ask patients who present with insomnia and fatigue about accompanying depressive symptoms. In addition, depression is often comorbid with, or can result from, other medical conditions, or due to the side effects of medications. In the DSM5, 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 SIGECAPSS 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 DSM5 criteria, to make a diagnosis of a depressive disorder.

The most recent (2009) US Preventive Services Task Force (USPSTF) guidelines



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 DSM5 criteria for major depressive disorder and persistent depressive disorder (dysthymia)

recommend screening children 12–18 and adults for depression when staff-assisted depression care supports are in place to ensure accurate diagnosis, effective treatment, and follow-up. "'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 DSM5, 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 DSM5.

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.

DSM5 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
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

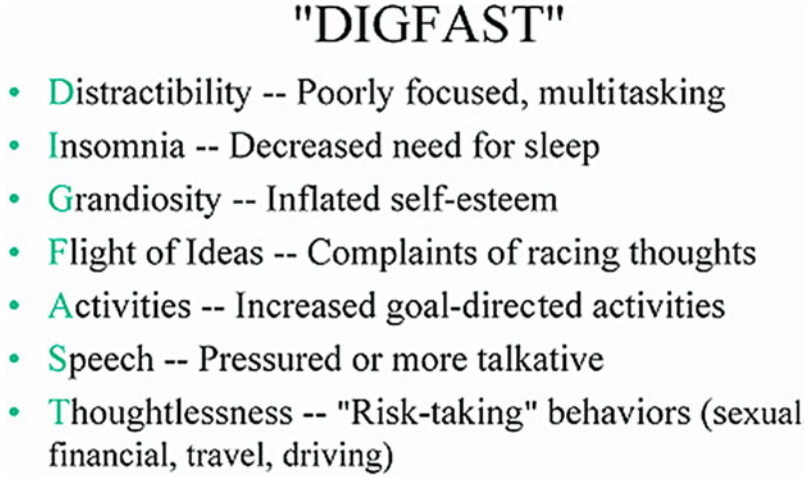
Bipolar II disorder consists of a pattern of recurring mood episodes consisting of one or more major depressive episodes and at least one hypomanic episode:

DSM5 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.

A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting at least four 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:

Fig. 3 DIGFAST



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 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.

Table 4. WHIPLASHED SCREEN for BIPOLAR DEPRESSION (8)

W	orse or "wired" when taking antidepressants
H	ypomania, hyperthymic temperament,* or mood swings by history
I	rritable, hostile, or showing mixed features during the presenting depression
P	sychomotor retardation appears to be more common in bipolar I depression than in unipolar major depression; however, several studies note that psychomotor agitation is more common in bipolar II than in unipolar major depression
L	oaded family history: Mood swings, bipolar disorder, alcoholism
A	brupt onset and/or termination of depressive bouts, or relatively brief depressive episodes (less than 2 to 3 months)
S	easonal or postpartum pattern of depression
H	yperphagia and hypersomnia
E	arly age at depression onset (younger than 25 years)
D	elusions, hallucinations, or other psychotic features

Note: More than 5 positive, go on to administer other assessment measures and DSM5 criteria to further diagnose bipolar depression

Fig. 4 WHIPLASHED screen for bipolar depression [8]

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 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. Nonpsychiatric 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 DSM5 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 settings 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?

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.

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 [12]. 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 [13].

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 non-response 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 has relegated these agents to a second-line use in most treatment plans when first-line medications have failed [14].

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 [14]. Recently the role of ketamine infusion has been explored in psychiatric clinical settings for severe depression with a rapid improvement in symptoms [15]. 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), tri-iodothronine, stimulants (i.e., modafinil), and hormone replacement (i.e., testosterone in men) [16].

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

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)
Trazodone (Oleptro)			+					Off label: aggressive behavior, etoh withdrawal, prevention of migraine

Mirtazapine (Remron)			+					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
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.

Table 2 FDA-approved medications for major depressive disorders [16]

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

Table 3 FDA-approved treatments for bipolar disorder [18, 19]

Acute mania	Acute bipolar depression	Bipolar maintenance
Lithium	Olanzapine/fluoxetine	Lithium
Chlorpromazine	Quetiapine, XR	Lamotrigine
Valproic acid, ER	Lurasidone[a]	Olanzapine
Olanzapine[a]		Aripiprazole[a]
Risperidone[a]		Quetiapine, XR (adjunct)
Quetiapine, XR[a]		Risperidone long-acting injection[a]
Ziprasidone		Ziprasidone (adjunct)
Aripiprazole[a]		
Carbamazepine, ECR		
Asenapine[a]		

[a]Adjunctive and monotherapy. ER, ERC, XR: extended release formulations

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 [17]. Therapeutic massage, physical exercise, meditation, and acupuncture/acupressure are also widely used with good effect but limited evidence [17].

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 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 [20]. 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 three agents have been approved for the treatment of bipolar depression. These include olanzapine + fluoxetine combination, quetiapine and quetiapine XR, and lurasidone. Of these, only quetiapine is approved to treat acute depression in patients suffering from bipolar II [21] and is the only medication 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 [22], 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 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 3 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, five 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 [23]. 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 [21].

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 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.)?" [24]. 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 [24].

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 [25].

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 [26]. Vagal nerve stimulation (VNS) is usually reserved for treatment-refractory cases, but has no positive RCTs proving its efficacy [13]. 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 [17].

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.

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 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 [27]. 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 [28]. 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 [29]. Postpartum depression is associated with impairment in the mother-infant attachment. Treatment has to weigh 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 [30]. Paroxetine has a “D” classification for safety in pregnancy and should be avoided in the first trimester.

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Family Medicine
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The Suicidal Patient

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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 suicidal ideations which include 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].

Epidemiology

In 2011, suicide was the 10th leading cause of death in the United States, accounting for the loss of nearly 40,000 lives. In the 15–34 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 [3].

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 [4]. Groups that perceive themselves to be socially isolated, such as homosexuals, are also at increased risk [5].

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 screening of asymptomatic persons [6]. Many patients who die by suicide have seen a healthcare provider in the preceding month [7]. 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.

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Table 1 Risk factors for suicide [9, 11]

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	
Environmental	
Recent loss of loved one	Access to means (such as firearms)
Exposure to suicide	Unemployment, or other financial stressors
Social stressors including isolation or recent humiliation	
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

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 [8]. Psychiatric disorders, especially depression with anhedonia and/or anxiety, bipolar disorder with a mixed episode, and personality disorders, also confer a significantly increased risk [9]. 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 [10]. 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 [12].

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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 [13]. 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 [14]. Direct inquiry about suicidal thoughts has also been associated with improved identification of those at risk for suicide [15]. 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 [6]. Furthermore, there is a paucity of data on what specific components should be included in a risk assessment in order to reliably predict suicide [16]. 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 [12].

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, etc.) should also be assessed. The assessment of suicidal ideation may include 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, etc., is important. This information then can be synthesized for the suicide risk formulation [12, 13]. 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 [13]. 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 past attempts, if there is a family mental health history, and what has kept them from engaging in self-harm [17, 18].

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

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Table 2 Risk categories for suicide [2]

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

Table 3 Suicide safety plan components [19]

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, etc.
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.
A list of social support resources (friends or family)
Removal of items that may be used to cause self-harm
List of resources such as crisis hotlines
Elicit any other resources that the patient might feel are helpful

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 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, 19].

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.

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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 [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 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 [20].

General Considerations

In addition to identification of at risk patients, several other strategies may be employed to prevent suicide and suicide attempts. Restricting access to lethal methods through firearms control, detoxification of domestic gas, the restriction of the sale of pesticides, and limiting access to certain medications have been effective in reducing suicide rates [21, 22]. Installing barriers at common jumping sites has also been shown to reduce death by suicide [23]. 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 [21, 22]. Community-based programs that integrate these principles, as well as promoting a system-wide approach to suicide prevention and supporting the implementation of

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comprehensive policy changes, have been successful in reducing suicide rates [24]. Media engagement in suicide prevention efforts can be accomplished through responsible reporting [21, 25]. 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 [22, 25].

Therapeutic Considerations

Several psychiatric disorders, including depression, are associated with an increased likelihood of suicide [9] (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 [26, 27].) Failure to optimize treatment of conditions such as depression contributes to many suicide attempts [21, 22], and initiation of therapy with SSRIs or tricyclic antidepressants has been shown to reduce rates of attempted suicide [28].

Psychotherapy for suicide attempters including cognitive therapy and interpersonal psychotherapy plays a role in reducing suicide attempts [29, 30]. 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 [31].

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 [32, 33]. 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 [32].

Follow-Up Care

Post-discharge follow-up contact plays an important role in decreasing suicide risk [34]. 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 [35] (see Fig. 1).

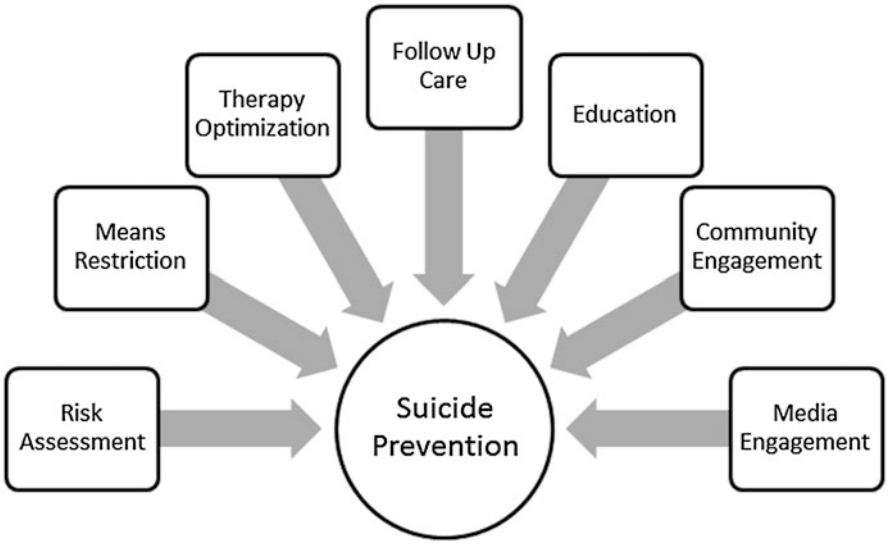

Fig. 1 Components of suicide prevention [20–22, 24, 25, 34]

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Emerging Environmental and Other Considerations

Emerging evidence supports several nontraditional suicide risk factors. Altitude has been proposed as a potential risk factor for suicide, presumably due to metabolic stress as a result of hypoxia [36]. Among elderly patients, lack of quality sleep seems to confer an elevated risk of suicide regardless of the presence of a mood disorder [37]. Chronic pain is an independent risk factor for suicide [38]. Similarly, glucocorticoid therapy appears to increase the risk of attempted or completed suicide [39]. Tobacco dependence and post-traumatic stress disorder (PTSD) are also emerging risk factors for suicide [40]. Recent prison release seems to be associated with increased suicide risk especially in the presence of comorbid mental illness or substance abuse [41]. 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 [42, 43]. These children are also at risk for hospitalization related to depressive and anxiety disorders as well as other psychiatric symptoms and social maladjustment [43]. 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 [44]. Of note, multilayered suicide prevention programs decrease the risk of moderate to severe family violence as well as overall risk for completed suicide [24]. Finally, the lifetime economic burden of suicide is great, costing in billions of dollars due to medical costs and lost productivity [45].

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Somatoform Disorders and Related Syndromes

Pamela Pentin and Lili Dofino Sperry

Contents

General Principles

Introduction

Somatoform disorders as a group cause significant physical and emotional distress. They impair occupational and social function. They are associated with increased work absences, more time spent in bed, a lower quality of life, an increased risk for iatrogenic injury, and increased healthcare utilization and costs. The accompanying impairment is comparable to that seen with mood and anxiety disorders [1]. Fortunately, effective treatment strategies exist that can improve somatoform conditions, reinforcing the importance of identifying and engaging affected patients. This remains true despite the challenges inherent in the nature of managing symptoms with no identifiable tissue pathology.

Background: Evolution of Psychosomatic Disorders in the DSM

Appreciation for the interplay between "psyche" and "soma" dates back to ancient civilizations. The psychosomatic synergy has been conceptualized in numerous ways throughout the history of medicine and psychiatry. The criteria for diagnosis in the DSM were originally derived from criteria developed by Perley and Guze for a polysymptomatic form of hysteria coined Briquet's syndrome [2]. Briquet's syndrome is now

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obsolete, but the historical context still infuses the new classification of somatization with disorders that reflect the past notion of "polysymptomatic hysteria," migrating medical providers toward a progressive skepticism of psychosomatic processes. The trend became even more pronounced as medicine became more evidence based within a biomedical model. But looking forward with large bodies of research now supporting psychosomatic medicine, the DSM-5 reflects a new and invigorated recognition of "psychosomatic processes."

The DSM-5 places particular emphasis on the role and influence of cultural factors on the experience of psychosomatic disorders. No single diagnostic label can accurately reflect the complexity of human disease or how distress is "embodied," and this in part led to the considerable changes in defining "somatoform disorders" in the current DSM-5. The DSM-IV disorders of somatization, hypochondriasis, pain disorder, and undifferentiated somatoform disorder have been removed and in most cases would now meet criteria for somatic symptom disorder (SSD).

The DSM-IV diagnosis of somatization disorders required a specific number of complaints from among four symptom groups. The SSD criteria no longer cite this requirement, simply requiring that somatic symptoms must be significantly distressing or disruptive to daily life and must be accompanied by excessive thoughts, feelings, or behaviors.

Another key change in the DSM-5 criteria is that an SSD diagnosis does not require the somatic symptoms to be medically unexplained. In other words, symptoms may or may not be associated with another medical condition. The DSM-5 narrative text description accompanying the criteria for SSD cautions "it is not appropriate to diagnose individuals with a mental disorder solely because a medical cause cannot be demonstrated." [3]

This change in emphasis removes the mind-body separation implied by DSM-IV and encourages clinicians to make a comprehensive assessment and use their clinical judgment rather than a checklist. The change also permits patients who suffer both SSD and another medical diagnosis to get the help they need.

Epidemiology

A large proportion of somatization encountered by the family physician is related to the presence of another psychiatric disorder, such as major depression or panic disorder. The Epidemiologic Catchment Area (ECA) study found that respondents with a lifetime diagnosis of somatization disorder had a much higher lifetime history of DSM-III panic disorder, obsessive-compulsive disorder, and major depression compared to those without a somatoform disorder. Since the ECA study there have been only sporadic population-based studies investigating this association. In most studies that do exist, a robust comorbidity between somatization and anxiety/depressive disorder was found. The comorbidity between somatization and other psychiatric and medical conditions has implications on treatment, and further studies of comorbidity will perhaps reveal the neurobiological underpinnings of somatoform disorders and help to determine whether these are independent entities or not [4].

Another variable that impacts incidence and prevalence is "care-seeking behavior." Community studies show that persons with somatization who seek health care have significantly more stressful life events and psychological distress and are more likely to meet criteria for depressive or anxiety disorders than those who do not seek out health care [5]. The ECA study found more than 50 % of persons reporting five or more medically unexplained symptoms met criteria for a psychiatric disorder, while only 5 % of respondents without these symptoms met criteria [6]. Further, the ECA study showed that community respondents with one or more psychiatric disorders were significantly higher utilizers of medical services than respondents without a psychiatric disorder.

The ECA study revealed that 58 % of those with a mental disorder had consulted their primary physicians in the past 6 months, twice as many as those without a mental disorder [7]. In fact, physical symptoms are a common diagnostic element of the clinical presentation of depression and anxiety; patients most commonly cite insomnia, pain,

fatigue, weakness, dizziness, dyspnea, palpitations, gastrointestinal complaints, paresthesias, tinnitus, and sexual dysfunction [8]. Also, there is a linear relationship between lifetime anxiety and depressive disorders and the number of current and lifetime medically unexplained symptoms [9]. It is critical to study comorbidity in the general population because it is so closely associated with treatment-seeking behavior [10]. More population-based longitudinal research will be needed to shed light on the temporal patterns of comorbidities and determine whether these are causal relationships or associations underlying risk factors.

Genesis of Somatization

The Stress-Diathesis Model

A number of theories have been postulated to explain the genesis of somatization, but there are two leading hypotheses. The first suggests that adverse childhood experiences contribute to the development of somatizing behavior by predisposing an individual to respond to stress somatically. The second hypothesis suggests that environmental stress leads to maladaptive communication of distress. In both theories *illness behavior* elicits care-giving responses from others and may direct attention away from other areas of conflict. Environmental influences include cultural attitudes that emphasize medical diagnosis and finding a "cure" for every affliction. Moreover, the severity of childhood adversity also seems to be associated with maladaptive high-risk behaviors such as smoking, drinking alcohol, and obesity, among other behaviors. Somatic symptoms have also been linked to personality traits such as neuroticism, harm avoidance, and high negative affectivity. Both learned and genetic origins for the traits of neuroticism and negative affectivity have been hypothesized [11]. Patients with personality disorders tend to have dramatic care-seeking behavior, and in some contexts being "sick" or in pain may be the only way to increase support from family members and medical providers and/or to attain financial stability.

Early Life Experiences

Adverse childhood experiences have a profound impact on the development of attachment styles, and these experiences can lead to somatoform behaviors. Insecure attachment, for example, is reflected in personality traits and interpersonal behaviors such as care-seeking behavior, which can be so maladaptive that it provokes hostility in others, further exacerbating care-demanding behavior [5]. Adverse childhood experiences can include childhood illness, parental illness, and childhood trauma. Substantial literature supporting the influence of social modeling on illness behavior [12] reflects how it can serve as a diathesis for maladaptive care-seeking behaviors.

Social Factors

How humans interpret and express any feeling or sensory perception is, in large part, determined by the social context in which it occurs, which in turn influences the responses of caregivers within the social system. The social context includes the influence of the health-care system on the "legitimacy" of the patient's condition (i.e., whether or not the individual is considered "sick"), and this in turn is influenced by medical provider attitudes, behaviors, and responses. Uncertainty of diagnosis, inadequate or excessive medical advice, or excessive reassurance may all contribute to the patient's beliefs. Many cultures stigmatize mental illness as being more volitional than physical illness. Carrying a diagnosis of a physical ailment removes stigma and legitimizes symptoms, allowing these symptoms to be "difficult or unable to treat." A physical diagnosis can thus increase functional disability and health-care utilization, making it an important public health concern.

Variations in prevalence of somatoform disorders may reflect the greater availability of, and greater patient faith in, high-technology diagnostic facilities and specialists in highly medicalized countries such as the United States [13]. Specialists are mainly concerned with detecting/excluding disease of the system they specialize in, rather than a global appraisal of the patient's ill health. Even when emotional disturbance is apparent, the

specialist will still often order an investigation to "exclude" a physical disease. Further negative investigations or treatment failures may then lead to another specialist referral and continued avoidance of the patient's emotional problems. The patient's access to specialist care is largely regulated by the primary care provider (PCP) who negotiates this care with the patient. This "gatekeeper" function of the PCP may also work at times to decrease the prevalence of somatization disorder. While the etiology of chronic somatization is poorly understood, somatization disorder cannot occur without medical complicity. So it is likely that the type of health-care system influences the prevalence of somatoform disorders [13].

A Biological Substrate for Somatization

New research suggests that many symptoms without identifiable pathology may be caused by disturbances in psychophysiologic brain-body pathways. An example of this is the abnormalities seen in smooth muscle tone in the gastrointestinal tract during stress in persons with irritable bowel syndrome [14]. Most recent research shows that the pathways are bidirectional. Changes in the brain secondary to stress cause functional abnormalities in the body and vice versa. Another example comes from the arena of chronic pain, where the ongoing pain experience creates pain memory which stimulates a large pain response region in the brain and ultimately a more intense pain experience.

The processes responsible for the association between subjective symptoms and inflammatory processes have been elucidated over the last decade [15, 16]. Associations between self-reports of fatigue and elevated inflammatory markers have been reported in patients with various diseases. A wealth of research has been conducted in the areas of cardiovascular disease and cancer, for example. The co-occurrence of decreasing energy, general malaise, and minor depression in the weeks that precede a myocardial infarction has been termed "vital exhaustion" [17]. Furthermore, high levels of inflammatory markers have been found in apparently healthy patients who score high on vital exhaustion [16]. The mechanism for this process is complex but can be summarized thusly: with inflammatory response, the brain's innate immune cells produce pro-inflammatory cytokines which are in turn responsible for the subjective and behavioral components of illness, which mediate the feeling of illness and thus the behavior of being ill. Studies of brain effects of cytokines show that, although cytokine-induced sickness behavior should resolve as the precipitant passes (e.g., an infectious process), the sickness behavior can persist when the innate immune system is chronically activated. This can culminate in major depression in vulnerable patients [18]. The same effect has been seen in patients whose hypothalamic-pituitary-adrenal axis is more responsive to their immune system [19]. The pathophysiology of immune-to-brain communication involves a cross-sensitization process of stressors and cytokines which likely plays an important role in somatic amplification.

The clinical relevance is again most obviously appreciated in the field of pain. The perception of pain is strongly amplified by the effect of pro-inflammatory mediators produced by activated glial cells in the spinal cord [20]. The medical implication of this mediation is that many somatized symptoms, including depressed mood, fatigue, and pain, may represent the expression of a previously sensitized brain cytokine system that is reactivated by infectious or noninfectious trauma.

At the therapeutic level, treatments that specifically target activation of the brain cytokine system are not yet available. However, evidence does exist to support pharmacological (e.g., antidepressants) and non-pharmacological (e.g., exercise) therapies that can attenuate somatic symptoms by downregulating inflammation [3].

Classification

The term somatization is commonly used in the medical literature and often defined as symptoms without organic cause. Reliance on a negative

definition has influenced how it is studied and classified. But the problem with the concept of psychogenesis is that psychological causation is sometimes believed to be an alternative to pathophysiologic causation, when in reality the two are probably synergistic.

Research findings argue against a defined dichotomy of patients meeting the criteria for the disorder or not meeting the criteria, but rather a spectrum of severity of somatization. As the number of symptoms increase, so do the psychological distress, the presence of depressive and anxiety disorders, and the degree of functional impairment. Controlling for demographic variables, medical utilization, disability, and concurrent DSM diagnosis, it seems that a spectrum of severity of somatization exists versus a qualitative break, once the criteria for somatization disorder are met [9, 11].

Conceptual Classification: A Continuum of Somatization

Distress and somatization are highly correlated [21]. As patients experience increasing distress, they develop multiple unexplained or disproportionately severe medical symptoms. This continuum manifests as acute and/or chronic presentations.

Acute Somatization

Difficult life events or circumstances tend to lead to psychological and physical discomfort, such as anxiety and nausea. Interestingly, throughout history and across cultures, it has been more common to express distress in somatic terms than in psychosocial terms (e.g., headache or abdominal pain) [22].

Stress-related symptoms account for a large percentage of visits to medical providers. Traditional techniques such as symptom management, reassurance, and a thorough history and physical diagnosis are generally adequate to address the patient's symptoms. Social support is known to provide a buffer between stress and distress [23], and individuals tend to seek support from their social system and from their physician. In most cases, distress resolves as the stressor resolves and there are no lasting sequelae. In the absence of a primary psychiatric condition, the diagnosis of adjustment reaction can be made to account for short-term residual sequelae.

Chronic Somatization

Unfortunately, there are many patients whose symptoms persist despite treatment of their acute or chronic medical and mental disorders and despite reassurance from their medical providers. This clinically "difficult" group often reflects a somatization disorder as well as other mental and organic conditions.

The severity and duration of somatization is intimately perpetuated by the medical system. The physician who orders invasive tests and treatment in pursuit of a biomedical diagnosis and cure may unintentionally promote somatizing behavior and lead to iatrogenic injury. Further complicating the picture, it can be difficult to diagnose, say, depression, when most symptoms can be accounted for by the presence of a medical condition. This difficulty is enhanced if somatization is considered only as a diagnosis of exclusion because treatable psychiatric factors magnifying the medical disorder can be missed.

Constellations

"Functional somatic syndromes" (FSS) have been used to label the constellation of symptoms that are grouped together for which no adequate medical explanation has been found. Every medical specialty has them: irritable bowel syndrome, chronic pelvic pain, tension headache, or atypical chest pain, among others. The FSS have many overlapping features but group into distinct enough clusters. Treatment of these is usually approached in the same way that somatization is, through multidisciplinary treatments that include pharmacological, behavioral, and lifestyle interventions.

DSM-5 Classification for Somatic Symptom and Related Disorders

The DSM-5 classification includes somatic symptom disorder, illness anxiety disorder, functional neurological symptom disorder, psychological

factors affecting medical conditions, and factitious disorder.

Approach to the Patient

The family physician is often presented with the patient who has a cluster of symptoms for which no medical explanation can found. These patients are responsible for a high percentage of visits to specialists [24]. A challenging variable is that patients with similar tissue pathology vary considerably in their perception of symptoms and degree of functional impairment. Some patients minimize symptoms and others amplify them. It is no surprise that comorbid psychiatric illness and stressful life events are associated with amplification. The tendency of patients with comorbid chronic medical and psychiatric disorders to amplify symptoms can be diagnostically challenging for physicians and often leads to excessive and unnecessary medical testing. The challenge resides in that distress and disease both produce physical symptoms. Symptoms cannot be split into the dichotomy of "somatogenic" and "psychogenic."

To deepen the understanding of the role of psychosocial influences of symptoms, greater attention should be placed on the process of somatization, which links the physiology of distress and the psychology of symptom perception. The primary care doctor should take into account that somatization frequently coexists with medical illness, that there is a spectrum of somatization severity from acute to chronic, and that most somatization is transient and treatable [25].

Diagnosis

Somatic symptom disorder (SSD) is characterized by somatic symptoms that either are very distressing or result in significant disruption of functioning, as well as excessive and disproportionate thoughts, feelings, and behaviors regarding those symptoms. To be diagnosed with SSD, the individual must be persistently symptomatic (typically at least for 6 months) [26].

Operationalization of the DSM-5 diagnostic criteria for somatic symptom and related disorders (DSM-5, pp. 309–327).

Screening questions: *Do you worry about your physical health more than most people? Do you get sick more often than most people?*

If yes, ask: *Do these experiences significantly affect your daily life?*

If yes, ask: *Which is worse for you, worrying about the symptoms you experience or worrying about your health and the possibility that you are sick?*

1. Somatic symptom disorder
   (a) Inclusion: Requires at least one somatic symptom that is distressing. *Do you experience symptoms that cause you to feel anxious or distressed? Do these symptoms significantly disrupt your daily life?*
   (b) Inclusion: Requires at least one of the following thoughts, feelings, or behaviors, typically for at least 6 months:
      i. Disproportionate thoughts: *How serious are your health concerns, and do you think about them often?*
      ii. Persistently high level of anxiety: *Do you persistently feel a high level of anxiety or worry about your health concerns?*
      iii. Excessive investment: *Do you find yourself investing a lot more time and energy into your health concerns than you would like to?*
   (c) Modifiers
      i. Specifiers
         - With predominant pain
         - Persistent
      ii. Severity
         - Mild: one symptom
         - Moderate: two or more symptoms
         - Severe: two or more symptoms plus multiple somatic complaints or one very severe somatic symptom
   (d) Alternatives
      i. If a person is focused on the loss of bodily function rather than on the distress a particular symptom causes, consider conversion disorder (functional

neurological symptom disorder) (full criteria are in DSM-5, pp. 318–319). The criteria for this disorder include symptoms or deficits affecting voluntary motor or sensory function, clinical evidence that these symptoms or deficits are inconsistent with a recognized medical or neurological disease, and significant impairment in social or occupational functioning.

ii. If a person has a documented medical condition other than a mental disorder, but behavioral or psychological factors adversely affect the course of his medical condition by delaying recovery, decreasing adherence, significantly increasing health risks, or influencing the underlying pathophysiology, consider psychological factors affecting other medical conditions (full criteria in DSM-5, p. 320).

iii. If a person falsifies physical or psychological signs or symptoms, or induces injury or disease to deceptively present himself to others as ill, impaired, or injured, consider factitious disorder imposed on self (full criteria in DSM-5, p. 324).

iv. If a person falsifies physical or psychological signs or symptoms, or induces injury or disease to deceptively present someone else to others as ill, impaired, or injured, consider factitious disorder imposed on another (full criteria in DSM-5, p. 325).

2. Illness anxiety disorder
   (a) Inclusion: Requires all of the following symptoms for at least 6 months and the absence of somatic symptoms:
      i. Preoccupation: *Do you find yourself unable to stop thinking about having or acquiring a serious illness?*
      ii. Anxiety: *Do you feel a high level of anxiety or worry about having or acquiring a serious illness?*
      iii. Associated behaviors: *Have these worries affected your behavior? Some people find themselves frequently checking their body for signs of illness, reading about the illness all the time, or avoiding persons, places, or objects to ward off illness. Do you find yourself doing those things or things like those?*
   (b) Exclusion: If a person's symptoms are better explained by another mental disorder, do not make the diagnosis.
   (c) Modifiers
      i. Subtypes
         • Care seeking
         • Care avoidant
      ii. Course
         • Transient
   (d) Alternatives
      i. If a person endorses symptoms characteristic of a somatic symptom disorder that cause clinically significant distress or impairment without meeting the full criteria for a specific somatic symptom and related disorder, consider unspecified somatic symptom and related disorder (see DSM-5, p. 327). If you wish to communicate specific reasons that full criteria are not met, consider other specified somatic symptoms and related disorders (see DSM-5, p. 327). Examples include brief somatic symptom disorder, brief illness anxiety disorder, illness anxiety disorder without excessive health-related behaviors, and pseudocyesis.

3. Factitious disorder
   Intentional production or feigning of physical or psychological signs or symptoms where the incentive is to assume the sick role and external incentives are absent

Differential Diagnosis

Once an organic cause has been ruled out or otherwise not found, where the sick role as incentive may be present and motivating behavior, the

main differential diagnosis includes factitious disorder (FD) and malingering (presenting with symptoms for secondary gain). The distinction between these can be difficult to establish, and the diagnosis of FD can only be confirmed if observation of symptom-producing behavior occurs or is admitted by the patient [26]. These scenarios are infrequent; therefore, diagnosis usually is made on a high index of suspicion.

Tips for Establishing the Diagnosis from a Differential

- Consider to what extent the signs and symptoms are intentionally produced.
- Consider to what extent the signs and symptoms are related to substances (current substance use makes a primary diagnosis difficult because of its impact on so many levels of physiology).
- Consider to what extent the signs and symptoms are related to another medical condition.
- Consider to what extent the signs and symptoms are related to a developmental conflict or stage (symptoms interfering with a normal developmental stage or causing conflict related to the stage such as affecting puberty or menopause or psychologic developmental stages).
- Consider to what extent the signs and symptoms are related to a mental disorder: "normality" covers a wide range of behaviors and thoughts that vary across cultures and developmental stages. A mental disturbance must cause "clinically significant disturbance and dysfunction" in an individual's life [27] to be considered a disorder rather than a constellation of symptoms.
- Consider whether no mental disorder is present: when a patient's symptoms and presentation do not fulfill the met criteria for a specific mental disorder but cause clinically significant distress or impairment, consider alternatives. For example, if the distress has developed as a maladaptive response to an identifiable psychosocial stressor, consider an adjustment disorder

Treatment

Patients with persistent symptoms with no identifiable pathology can respond to antidepressant medications as well as cognitive-behavioral therapy [28]. It is important to develop simple, feasible, and effective interventions that can be delivered through primary care by providers without specialized psychiatric skills.

Level I Evidence Based on Systematic Reviews

Antidepressant Medication

In a review conducted by O'Malley et al., 94 randomized controlled trials compared medications typically used for depression, for the treatment of somatoform disorders: tricyclic antidepressants, SSRIs, non-antidepressant medications, and placebo. Most trials showed improvement with any and all antidepressant medication interventions. O'Malley's group concluded that multiple medications can be effective treatment for somatoform disorders [29]. However, the authors cautioned that high study withdrawal rates were seen, and few studies reported on the side effects that could potentially contribute to withdrawal from the study.

Psychological Treatment

Cognitive-behavioral therapy (CBT) is the most extensively studied intervention for somatoform disorders. A meta-analysis demonstrated that either individual or group therapy can be effective in reducing physical symptoms and psychological distress, as well as in improving functional status [28]. Interestingly, benefits in the reduction of physical complaints occurred whether or not psychological distress was ameliorated. Future studies may help determine the optimal timing and duration of CBT and may identify those patients most likely to accept and respond to therapy.

Psychodynamic psychotherapy, family therapy, and other forms of psychological therapy such as reattribution and problem-solving approaches have not been studied thoroughly. However, case studies and series of these interventions have been published suggesting some improvement in somatization symptomatology. However, the evidence remains scarce making it difficult to generalize the results.

Comprehensive Management

In summary, there is good evidence to suggest that the treatment of somatization can be effective at the primary care level and that various modalities of treatment can be effective, specifically CBT and antidepressant medication. Moreover, physicians can play an important role in breaking self-defeating cycles of behavior. Recognizing somatizing behavior and understanding its genesis may allow physicians to assume a more empathetic stance with difficult patients, particularly because research and experience support that patients with somatization truly suffer. Their suffering may not correlate with "tissue pathology" but they experience distress nonetheless from somatic fixation.

Principles for a Biopsychosocial Approach to Somatic Fixation

1. Use a biopsychosocial approach from the beginning.
   (a) Include psychosocial questions in the interview.
   (b) Proceed with a reasonable but appropriately limited medical work-up.
2. Ask about symptoms without letting symptoms guide the visit.
3. Develop a collaborative relationship that maintains patient engagement.
   (a) Suggest keeping a symptom diary.
   (b) Clarify expectations and do not promise easy answers.
   (c) Consider involving pertinent family members to enhance psychosocial input.
4. See the patient at regular intervals and discourage visits to other providers unless for a specific referral.
   (a) Schedule regular appointments not dictated by symptom occurrence or intensification.
   (b) When a referral is indicated, contact the consultant beforehand and be specific about the referral questions.
5. Negotiate a mutually acceptable diagnosis.
   (a) Elicit the patient's and family's thoughts about the diagnosis.
   (b) Explore what the diagnosis or symptoms mean to the patient.
   (c) Ask about expected treatments and outcomes.
   (d) Develop a treatment plan with the patient and family.
6. Ask about any stressful life events, challenges, or unresolved family problems, such as a history of abuse and/or trauma, unresolved grief, forms of over-functioning, and substance use abuse.
7. Invite the family to participate in the management of treatment, as below:
   (a) Request each person's observations and opinions.
   (b) Try to elucidate if the illness has changed the typical roles or balance of power in the family.
   (c) Try to understand any marital or transgenerational meaning of the symptoms.
   (d) Ask what each person is doing to help.
   (e) Ask how family life would be different if the patient were asymptomatic.
8. Emphasize the patient's and the family's strengths and areas of competence.
9. Avoid psychosocial fixation maintaining an integrated approach; use biomedical explanations that also have psychosocial meanings (e.g., stress, depressed immune system).
10. Monitor both the patient's and your own discomfort with uncertainty.

11. Assess progress by monitoring changes in the level of function rather than in symptoms.
12. Terminate the intensive phase of treatment slowly.

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Selected Behavioral and Psychiatric Problems

Amy Crawford-Faucher

Contents

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 manage the patient medically.

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

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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 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 5th 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,

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] and [8]

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. Comprehensive eating disorder centers use a variety of protocols, but many include nasogastric 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 three 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 fully or partially resolve within 5 years of diagnosis, but up to 20 % may become chronic [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 USA of 2–3 %. It occurs with similar frequency in many other high-income countries. The underlying risk factors are similar to 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 disorders are distinct.

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.

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] and [8]

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 [11].

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 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 arise 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 a 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 damaging 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 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 and as children and adolescents may have been loners who had poor peer relationships and may have been teased. 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 –

0.6–3 % – 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" and devalue them when the perceived support is not sufficient. 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, many of these medications require monitoring and can have significant side effects.

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 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,

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 [20–22]

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.

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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Autism Spectrum Disorders

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General Principles

Definition/Background

Autism Spectrum Disorder (ASD) is a continuum of neurodevelopmental conditions distinguished by deficits in social communication and interaction with restricted, repetitive, and/or stereotyped patterns of behavior, activities, and interests. Dr. Leo Kanner first described early infantile autism in 1943 [1]. The ASD social deficits and behavioral patterns are usually apparent in early childhood but may not be recognized until they interfere with other social, educational, or occupational life functions.

Pathogenesis/Genetic

Although no single chromosomal abnormality or genetic mutation has been identified as causing ASD, strong evidence exists that ASD has a genetic component. ASD is more prevalent in ASD siblings and has a high concordance rate among monozygotic twins [2]. Further support for a chromosomal connection is the dissimilar sex distribution wherein males outnumber females 4–5 to 1. Genetic counseling and testing have a diagnostic yield of 30–40 % and should be discussed with ASD patients and families [3]. About 10 % of ASD patients have a known genetic condition (e.g., fragile X syndrome, tuberous sclerosis, or Rett syndrome) [4].

Pathogenesis/Neurobiological

Structural, functional, and environmental influences contribute to the development of ASD. ASD patients frequently have macrocephaly with 25 % having a head circumference greater than the 97th percentile. A trajectory of accelerated head growth during infancy later stabilizes. Increased neurons in the prefrontal cortex have been noted as have alterations in the prefrontal and temporal cortex organization. Neural connectivity and synaptic formation and activity abnormalities are also hypothesized. Functional abnormalities occur in connectivity patterns, serotonin synthesis, methods of processing, and deficits recognizing and understanding speech.

Environmental factors may affect underlying genetic and structural predispositions toward the development of ASD. Risk factors include increased maternal or paternal age, low birth weight, maternal metabolic conditions such as diabetes and hypertension, and exposure to valproic acid. Antenatal exposure to selective serotonin reuptake inhibitors (SSRIs) confers little or no risk of ASD. Vaccines, notably MMR, and thimerosal are not causally related to ASD [5].

Epidemiology

The prevalence of ASD has increased over the last five decades. Previously estimated to be 0.5 per 1,000 children, more recent studies report ASD prevalence to be 10–20 per 1,000 children. The Autism and Developmental Disabilities Monitoring Network (ADDM) is an active surveillance system in the United States collecting data on ASD prevalence in children aged 8 years from health and education records.

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The 2010 ADDM report estimated a prevalence of 14.7 per 1,000 children, although the rate varied from 5.7 to 21.9 per 1,000 children over the 11 reporting sites. The overall rate is 1 in 68 children or 1 in 42 boys and 1 in 189 girls [6]. The reported data cannot serve as the actual prevalence of ASD in the United States [7]. While some of the prevalence increase is attributable to improved awareness and recognition, changes in diagnostic reporting practices account for much of the increase [8].

ASD prevalence is increased in siblings of children with ASD. Previously, the recurrence risk was estimated at 3–10 %, but more recent studies report 11–19 %. If two or more siblings have ASD, the recurrence risk is 33–50 % [9].

Although considered a pervasive developmental disorder, nearly half of ASD children have intelligence in the average range. Signs of ASD are often present before 18 months of age; however, the median age of ASD diagnosis is 53 months. The average interval between first documented evaluation and diagnosis is 13 months. Children with less disability are often diagnosed at a later age.

The American Academy of Pediatrics recommends universal screening at 18 and 24 months of age [10]. Early potential predictors of ASD are poor attention to human faces by age 6 months, little infant-parent interaction by age 12 months, and reduced flexibility in control of visual attention by age 7–14 months.

Classification

The *Diagnostic and Statistical Manual*, Fifth Edition (DSM-5), provides criteria for ASD diagnosis [11] (see Table 1). DSM-5 recommends assigning three levels of severity (requiring support, requiring substantial support, requiring very substantial support) for each domain of social communication/interaction and repetitive/restrictive behavior. DSM-5 further recommends specifying the presence or absence of intellectual impairment; language impairment; known medical or genetic conditions; other neurodevelopmental, mental, or behavioral disorders; and catatonia.

Approach to the Patient Evaluation

The impairments inherent to ASD make the correct approach vital to having an accurate diagnosis and subsequent management. Whether the evaluation is initiated after routine screening at a well-child visit or after parents vocalize specific developmental concerns, a posture of therapeutic attention to the family's questions and a favorable clinical environment are critical to an accurate assessment. A number of preparations increase the precision of the evaluation. A quiet examination room without loud equipment or clutter, avoidance of rooms with bright or fluorescent lighting, and understanding any triggers as communicated by the parents may serve to decrease overstimulation. Moreover, communication of these techniques to the staff has the potential to facilitate consistency and increase the chance of an effective evaluation [12, 13].

Diagnosis

Clinical Evaluation

At well-child visits, use validated screening tools and employ developmental surveillance. The Modified Checklist for Autism in Toddlers Revised with Follow-up (M-CHAT R/F) is essential to the early detection of children with developmental issues [10, 14, 15] (see Table 2). However, while validated, these tools don't replace the indispensible practice of offering a listening and responsive ear to concerned parents who report atypical behaviors. Upon discovery of developmental concerns or pursuant to reported

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Table 1 DSM-5 diagnostic criteria for autism spectrum disorder (299.00)

A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history (examples are illustrative, not exhaustive):
1. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate of respond to social interactions
2. Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication
3. Deficits in developing, maintaining and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers
B. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history (examples are illustrative, not exhaustive):
1. Stereotyped of repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypes, lining up toys or flipping objects, echolalia, idiosyncratic phrases)
2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat same food every day)
3. Highly restricted, fixated interests that are abnormal in intensity of focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed of perseverative interests)
4. Hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment (e.g., apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights, or movement)
C. Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life)
D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning
E. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level

Note: Individuals with a well-established DSM-4 diagnosis of autistic disorder, Asperger's disorder, or pervasive developmental disorder not otherwise specified should be given the diagnosis of autism spectrum disorder. Individuals who have marked deficits in social communication, but whose symptoms do not otherwise meet criteria for autism spectrum disorder should be evaluated for social (pragmatic) communication disorder

parental observations, an evaluation incorporating a multidisciplinary team should be initiated to confirm diagnosis, exclude other etiologies (see Table 3), and determine the presence of any comorbid conditions. It is appropriate to initiate specific behavioral interventions based on the patient's symptoms and parental concerns while awaiting a definitive diagnosis [14, 16].

When ASD is suspected, referral to developmental services is appropriate even prior to confirmation of ASD. More focused recommendations such as referral to a supervised community playgroup, administration of a temperament scale, or use of picture books, naming of objects, and storytelling may be reasonable depending on the nature of the parent's report.

History and Examination

Once a child screens positive for ASD, pursuit of definitive diagnosis is imperative. While this is typically a prolonged multidisciplinary process, the physician can expedite initiation of treatment and support for the patient and family. This process begins with a thorough and directed patient and family history.

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Table 2 M-CHAT-R™ questions

1. If you point at something across the room, does your child look at it?
2. Have you ever wondered if your child might be deaf?
3. Does your child play pretend or make-believer?
4. Does your child like climbing on things?
5. Does your child make unusual finger movements near his or her eyes?
6. Does your child point with one finger to ask for something or to get help?
7. Does your child point with one finger to show you something interesting?
8. Is your child interested in other children?
9. Does your child show you things by bringing them to you or holding them up for you to see – not to get help, but just to share?
10. Does your child respond when you call his or her name?
11. When you smile at your child, does he or she smile back at you?
12. Does your child get upset at everyday noises?
13. Does your child walk?
14. Does your child look you in the eye when you are talking to him or her, playing with him or her, or dressing him or her?
15. Does your child try to copy what you do?
16. If you turn your head to look at something, does your child look around to see what you are looking at?
17. Does your child try to get you to watch him or her?
18. Does your child understand when you tell him or her to do something?
19. If something new happens, does your child look at your face to see how you feel about it?
20. Does your child like movement activities?

A successful history begins by preparing questions and the environment for the evaluation. The interviewer should query the caregiver while always engaging and addressing the patient as much as possible. Use of distraction techniques (e.g., toys, television, or music) and the establishment of the patient's level and style of communication can facilitate this evaluation. For instance, asking "yes/no" questions or allowing the patient to demonstrate various developmental skills can elucidate the most effective means of obtaining historical accuracy.

ASD symptoms are commonly noted in the second year of life, but suspicion may develop earlier [17, 18]. According to DSM-V (see Table 1), symptoms must be present in the early developmental period though they may not be apparent until later when social demands exceed limited developmental capacity [11]. In fact, in less severe phenotypes, parents or teachers may not identify ASD until 4–6 years of age [19].

The history should focus on the DSM-V's ASD description and the presence of comorbid conditions. Questions regarding the categories of social impairment, any repetitive behavior patterns, their perceived impact on function, and overall severity are all helpful. Family history is important given the strong genetic component to ASD. The presence of the following conditions in family members should be noted: ASD, language delay, intellectual disability, fragile X, Angelman syndrome, Rett syndrome, Prader-Willi syndrome, tuberous sclerosis, Smith-Lemli-Opitz syndrome, mood disorder, seizures, OCD, schizophrenia, or tic disorders [20] (see Table 3). Moreover, ask about historical social data focused on stressors, specifically trauma and family supports [21].

A carefully conducted physical examination will identify comorbid conditions. Observing the patient's behavior adds valuable insight and critical diagnostic information more than a typical physical examination. An attentive clinician, concurrently with obtaining the history from the caregiver and patient, can glean this type of observation.

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Table 3 ASD differential diagnosis

Condition	Characteristics	Diagnostic testing
Global developmental delay/intellectual disability	Delay includes motor, speech, social, and intellectual components	MRI Cytogenetic screen/FraX Consider metabolic testing, subtelomeric arrangements tests, and rule out Rett syndrome
Social (pragmatic) communication disorder	Concerns limited to appropriate use of language	Advanced clinical evaluation may reveal if secondary to ASD or a primary pragmatic d/o
Developmental language disorder	Delayed language development with normal social interactions	Multidisciplinary assessment rules out ASD Formal hearing assessment to rule out hearing impairment
Language-based learning disability	Difficulty reading and writing	Speech language pathologist evaluation
Hearing impairment	Difficulty hearing spoken words Delayed language development	Formal audiometry
Landau-Kleffner syndrome	Acquired Primarily RECEPTIVE language regression	EEG specific changes MRI
Rett syndrome	Females Dramatic loss in speech and meaningful hand use after 6–18 months Deceleration of Head Growth	Genetic Testing for X-linked gene encoding methyl-CpG-binding protein 2 (*MECP2*)
Severe early deprivation/ reactive attachment disorder	Slow growth Withdrawn behavior Difficulty bonding with caregivers	History and physical exam concentrating on prior caregivers experiences
Social anxiety disorder	Minimal deficits in communication	Advanced clinical evaluation
Obsessive-compulsive disorder	Presence of obsession (ego dystonia) not just ritual and repetitive behaviors Minimal deficits in communication	Advanced clinical evaluation may reveal OCD as primary diagnosis or comorbidity with ASD

Impaired social communication is a hallmark of ASD. Delays and deviation in language development and diminished intent to communicate are frequently part of the initial presentation and may be noted during the clinical interaction. The child may have limited ability to show empathy or even awareness of other children. Individuals with ASD often lack joint attention – the ability to share interest, amusement, or attention with others. These patients commonly ignore nonverbal communication and have difficulty employing these cues or techniques. This further limits social interaction as their sense of boundaries and appropriateness is limited.

The second ASD component is the tendency toward restricted and repetitive behaviors. Certain repetitive, stereotyped motor mannerisms may be observed in the clinical setting, particularly if the child becomes uncomfortable during the exam. Individuals with ASD have difficulty with changes in normal routine, preoccupation with stereotyped or restricted interests, and tend to have aberrant processing abilities with regard to certain sensory or perceptual stimuli. Altered sensory perception may include preoccupation with licking nonfood objects, apparent indifference to pain, resistance to being touched, strong preference for certain textures, hypersensitivity to certain sound frequencies, and visual inspection of objects out of the corner of the eyes. Because these behaviors are difficult to capture in real time, a diagnostic tool with good sensitivity and high specificity may add value to the physician's clinical judgment [10]. However, given varying levels of scientific validation, the results should be correlated with the DSM-V diagnostic criteria and the entire patient context.

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Beyond the behavioral observation, evaluation of growth parameters, a skin examination, attention to dysmorphic features, and a neurological evaluation are part of the physical assessment. Approximately one fourth of children with ASD have a head circumference greater than the 97th percentile. Children whose repetitive behaviors affect diet or food consumption may show aberrant height or weight trajectories. Examination of the skin with a Wood's lamp may reveal the presence of hypopigmented macules consistent with tuberous sclerosis complex. Patients with ASD may have gait abnormalities, clumsiness, toe walking, or hypotonia [11].

Additional Evaluation

Once the diagnosis of ASD is confirmed, additional evaluation will be necessary to identify the presence of comorbid conditions and definitively exclude conditions in the differential diagnosis [22] (see Table 3). Although present in a minority of cases, a number of genetic conditions are associated with ASD with the most common being tuberous sclerosis complex, fragile X syndrome, and Angelman syndrome. Comorbid genetic conditions tend to be clustered in the subset of ASD patients with global developmental delay or intellectual disability. As such, it is reasonable to offer testing with chromosomal microarray (CMA) and DNA analysis for fragile X to all patients diagnosed with ASD. Further genetic testing, neuroimaging, metabolic testing, and EEG may be appropriate depending on the variables of gender, patient history, family history, and physical characteristics [3, 23]. Conversely, testing for yeast metabolites, gut permeability, nonlead heavy metals, trace elements, micronutrients, and immune abnormalities is not indicated regardless of presentation as no data support such analysis [24].

Treatment

ASD treatment must be individualized and multidimensional. Treatment will vary for pre- or nonverbal children versus verbal children, adolescents versus adults. The treatment goals are to reduce detrimental behavior, increase social skills, improve cognitive ability, and facilitate the child's development [25].

While ASD is considered a biological condition, the most effective treatments are behavioral and educational [26]. An excellent review of behavioral treatments has been published [27]. Medications have a minor role and do not address the core symptoms.

Behavioral Therapy

Behavioral therapy is most effective when it is applied early and is intensive in scope [28, 29]. The applied behavior analysis (ABA) method serves as the origin for behavioral therapy [30]. The Early Start Denver Model emphasizes developmental issues and relationship improvements [31]. This model enables development of intelligence, communication, and adaptive function and some improvement in language, daily living skills, and socialization. A pilot study found the earlier intervention is begun, the more the symptoms were reduced at age 36 months [32].

A less well studied approach uses structured teaching from the Treatment and Education of Autistic and Related Communication-handicapped Children (TEACCH) Model. Neither ABA nor TEACCH have evidence of superiority and may be more complementary than opposite [33]. In fact, the primary consumers of these services (parents, special educators, and administrators) favor a combination of approaches [33].

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Specific Domains

In addition to these broad treatment approaches, treatment of specific cognitive behavioral domains can be done. Nonverbal children could benefit from the Picture Exchange Communication System (PECS) [34]. Language development may be helped by joint attention on engagement training [35]. For toddlers, social synchronous engagement can be effective [36].

What Is a Comprehensive Intervention Program?

Comprehensive intervention programs address social communication, deficits in language ability, development of play skills, approaches to reduce maladaptive behaviors, and ongoing parental education [34]. Guidelines for nonmedical intervention are a guide to therapeutic interventions [34]. These guidelines indicate that

- ASD individuals should receive a comprehensive intervention within 60 days of ASD identification.
- The intervention must be individualized to the strengths and deficits of the individual.
- The program must address family concerns and offer opportunities for active family participation.
- The intervention should involve the individual a minimum of 25 h a week.

Specific guidelines to address social skill deficits include the following:

- Interventions targeting deficits in social communication and social skills should be offered to every ASD patient.
- Individuals with less verbal skills or whose language skills do not improve should be offered use of PECS.
- If PECS is unsuccessful, augmentative and alternative communication interventions should be considered.
- Auditory integration therapy is not recommended to address core deficits.

All intervention programs should include a baseline assessment and periodic follow-up assessments with a reliable and valid instrument. Consumers of autism services are vulnerable to unsupported effectiveness claims [37].

Vocational intervention is critical for transition into adulthood, but few randomized trials have been reported [26]. Therefore, no specific treatment recommendation can be made. Employment assistance should be offered to patients who have difficulty obtaining or maintaining a job.

Parental involvement in the behavioral treatment program is vital and has the advantage of bringing treatment into the home. This not only can benefit the child but may increase parents' and other caregivers' self-confidence [38].

Sensory integration therapy is often part of occupational therapy and may be one component of a more comprehensive program. Because its effectiveness has not been established, it is not a routine intervention [39].

Specific Behavioral Concerns

Irritability and Aggression

If behavioral therapy does not adequately control irritability or aggression and it is preventing the child from becoming socially functional, medication may be helpful (Table 4). Risperidone and aripiprazole are FDA approved for ASD-related symptoms. Using the Aberrant Behavior Checklist, risperidone decreased irritability [40].

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Table 4 Medications used with ASD

Behavior	Medication	Dosage	Adverse effects
Irritability, aggression	Risperidone Aripiprazol [40]	0.5–3 mg/day 2–10 mg/day	Weight gain, sedation, tremor, akathisia, extra-pyramidal syndrome, orthostatic hypotension, tachycardia, neuroleptic malignant syndrome
Repetitive behavior	Risperidone Aripiprazol [40] SSRI (multiple)	0.5–3 mg/day 2–10 mg/day Off-label unless OCD	As above As above Insomnia, agitation, disinhibition, dry mouth, headache, sexual dysfunction
Hyperactivity and inattention (ADHD-like symptoms)	Stimulants Atomoxetine Alpha-agonists (clonidine off label, guanfacine)	Multiple 0.5 mg/kg × 3 days, then 1.2–1.4 mg/kg/day Clonidine 0.1 mg Guanfacine 0.5–2 mg/day	Poor appetite, weight loss, irritability, insomnia Insomnia, orthostatic hypotension Hypotension, bradycardia, somnolence, dry mouth, irritability, constipation
Altered sleep – initial insomnia	Melatonin	0.3–6 mg/day	Headache, dizziness, nausea

Hyperactivity and Inattention

ASD children may have ADHD-like symptoms of hyperactivity and inattention. Stimulants and atomoxetine have limited benefit; however, they may produce more adverse events than in patients with ADHD [41].

Repetitive Behaviors

Repetitive behaviors are a common manifestation of ASD. Their presence does not always require treatment. If the behavior is interfering with social function or has not responded to behavioral intervention, medication could be appropriate.

The primary medications are risperidone and aripiprazole. While somewhat effective, caution is urged due to adverse outcomes. The selective serotonin reuptake inhibitors (SSRIs) have been used, but their efficacy is questionable [42].

Altered Sleep

ASD children may experience difficulty getting to sleep and at times staying asleep. Sleep disturbances can be very exhausting for the parents. The initial treatment would be improved sleep hygiene. This would include a consistent time going to bed, getting up, and having a common bedtime routine each night. A guideline is available for parents; however, it is not clear how effective these techniques are in improving sleep [43]. In a systematic review, melatonin did have some benefit. It provided about 70 min of overall sleep improvement and an earlier sleep onset of 66 min [44].

Prognosis

ASD patients have a two to eight times increased mortality risk. Higher intellectual ability has a better social prognosis. However, even without intellectual disability, occupational potential is usually limited.

Some patients will develop normal social communication, have few autistic symptoms, and have the diagnosis reversed, although rarely. The long-term outcome for much older ASD patients is currently unknown.

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Parents and usually mothers of ASD children will often experience depression and anxiety when their child is diagnosed with ASD as their role evolves from parent to advocate and often to therapist [45]. Some work is being done to help address these issues with mothers [46].

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Family Medicine
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Common Allergic Disorders

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Allergic diseases constitute a wide range conditions from allergic rhinitis to eosinophilic asthma, sharing immune-mediated pathophysiology, typically IgE mediated. Unlike chronic autoimmune diseases such as systemic lupus erythematosus, common allergic diseases tend to have an acute episodic presentation often precipitated by an environmental allergen.

Allergic Rhinitis

General Principles

Definition and Background

Allergic rhinitis is defined as a disease characterized by clear nasal discharge, nasal itching, sneezing, and airflow obstruction, due to IgE-mediated inflammatory reaction to inhaled allergens. In some cases, fatigue and malaise may occur in addition, leading to the common labels "hay fever" or simply "allergies." Typical allergens commonly implicated in allergic rhinitis include plant pollens, molds, dust mites, pet dander, and house pests. Commonly coexisting conditions include asthma, allergic conjunctivitis, atopic dermatitis, and obstructive sleep disorders.

Epidemiology

Allergic rhinitis is a highly prevalent condition that affects 15–30 % of population, with a higher burden of over 40 % in some areas [1]. The prevalence peaks in the teenage years to 40s, decreasing slowly in older age groups. Disease burden is possibly higher in childhood but is difficult to determine due to frequent upper respiratory tract infections and inability to self-report symptoms in this age. Epidemiologic variation seems to stem from geographic allergen distribution, reporting of symptoms, as well as heterogeneity in the disease itself. Even with the differences in regional prevalence, its incidence is increasing worldwide [2].

With its high prevalence, allergic rhinitis is a leading cause of productivity loss at work and school. The direct costs in the United States alone range from US$2–5 billion per year, a majority of which are drug prescriptions [3]. Allergic rhinitis often aggravates coexisting asthma and chronic sinusitis generating additional healthcare costs. The magnitude of disease burden is indicated by the very high volume of clinic visits and prescriptions needed for patients with allergic rhinitis: The indirect costs incurred by patients and their families stem from impaired productivity at work and school [4]. Some estimates place allergic rhinitis as causing a greater loss of productivity than any other disease, accounting for one-fourth of all lost productivity. The number of school days missed by children, either directly or indirectly due to allergic rhinitis, is around 800,000 to 2 million in the United States.

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Classification

Allergic rhinitis as a condition involving the nasal mucosa and upper airways classifies as a disease of the respiratory system. Further sorting into subcategories by specifying the triggering allergen aids in accurate diagnosis and treatment. Thus, allergic rhinitis may be listed as due to pollen, food, animal (cat or dog) hair and dander, and other allergen or, if allergen remains unknown, as cause unspecified. In patients with coexisting bronchial asthma, listing asthma as the primary diagnosis is recommended.

Allergic rhinitis is also subdivided into seasonal or perennial and intermittent or persistent. Seasonal allergic rhinitis, as the name implies, occurs during specific periods in the year such as spring or summer, typically linked to pollen production by plants in the geographic region, while symptoms of perennial allergic rhinitis can occur throughout the year being associated with persistent environmental allergens such as dust mites and house pests. Allergic rhinitis is considered intermittent if exposure or symptoms occur less than 4 days per week or less than 4 weeks per year [3]. If exposure or symptoms exceed these durations, the term persistent is applied. The distinction between intermittent and persistent helps gauge disease severity and guides treatment selection. Severity of allergic rhinitis is classified into mild and moderate to severe [5].

Approach to the Patient

The diagnostic approach to the patient with suspected allergic rhinitis consists primarily of careful history-taking 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 fairly straightforward. More commonly, patients tend to have no clearly identifiable triggers from history. Coexisting allergic disorders such as atopic dermatitis and asthma as well as a family history of these or allergic rhinitis itself support the diagnosis of allergic rhinitis in the patient.

Diagnosis

History

The chief symptoms of allergic rhinitis are nasal congestion, 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 pet dander and pollen. Others may indicate certain seasons coinciding pollen production, in which their symptoms tend to cluster; however, year-round pollen production can lead to perennial symptoms. Nasal discharge is typically watery in allergic rhinitis.

Patients often times complain of problems caused by posterior nasal discharge or postnasal drip. These troublesome symptoms include spasmodic cough, frequent throat clearing, coughing spells when talking, a sensation of choking, and aspiration of postnasal drip. Such symptoms may interfere with the quality of sleep. Hyposmia or anosmia is a common association.

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 be 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" and attributed to congestion in the veins of the eyelid. Repeated upward rubbing of the nose

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may cause a horizontal skin crease over the lower part of the nose. Physical examination may uncover coexisting asthma or atopic dermatitis.

Laboratory and Imaging

Plain x-rays of the sinuses are not recommended. Radiological imaging does not provide any specific diagnostic information relevant to allergic rhinitis. Imaging of the nasal sinuses and adjoining structures via computed tomography (CT) or magnetic resonance imaging (MRI) is indicated when complicated chronic sinusitis with extension of infection, nasal polyposis, or a neoplasm is suspected.

Special Testing

Proof of allergen sensitivity is not needed to start empiric treatment in patients with a likely diagnosis of allergic rhinitis. Allergy to an antigen is a clinical diagnosis. 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 treatment is inadequate; when the diagnosis is unclear, to guide therapeutic adjustments; or when knowing the specific allergens could alter treatment recommendations.

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 the skills and equipment needed to perform skin testing are not needed. On the other hand, skin testing yields results without having to wait for the laboratory report and is less expensive. Nevertheless, as discussed above, the vast majority of patients with allergic rhinitis can be diagnosed and managed without allergen testing.

Skin testing requires technical skills of introducing specific allergens into the skin and observing for a wheal and flare response. 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 used. 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 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 with careful history-taking enquiring about the presence of environmental triggers and sick contacts.

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Chronic sinusitis, more accurately referred to as chronic rhinosinusitis and a potential [6] 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 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 [7]. 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. Again, 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

Allergic rhinitis burdens patients and their families with considerable psychosocial difficulties due to its impact on quality of life. Reduced cognitive function affecting learning and work, impaired decision-making ability, and decreased self-esteem have been noted in these patients. Increased rates of learning disorders, attention, and conduct deficits [8] impair children with allergic rhinitis in particular when obstructive sleep disorder [9] and asthma are coexistent. Family physicians should be cognizant of these issues in discussing a holistic approach to managing this condition.

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

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
Nasal antihistamines	Azelastine, olopatadine	Mild to moderate	Bitter taste, epistaxis, sedation, burning sensation
Oral decongestants	Pseudoephedrine, phenylephrine	Mild	Agitation, gastrointestinal disturbances, insomnia
Topical nasal decongestants	oxymetazoline	Mild to moderate	Rebound nasal congestion, rhinitis medicamentosa
Oral antileukotrienes	Montelukast	Mild	
Immunotherapy	Specific subcutaneous/sublingual allergens	Moderate	Allergic reactions including anaphylaxis

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multiple methods is 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 limited or no improvement in symptoms.

Medications

Approach to Pharmacologic Treatment and Combination Medication Use

Severity and frequency (intermittent vs. perennial presence) of symptoms should guide medication selection (Table 1), with intranasal steroids being preferred for more severe cases over antihistamines. Second-generation antihistamines are recommended for regular use based on high-quality evidence, although short-term usage can be helpful in intermittent symptoms. Adding an intranasal steroid spray as needed may be effective during times of increased symptoms while antihistamines as an add-on to topical steroids remain unproven [10]. Switching to a different antihistamine sometimes seems to work in patients who are refractory to the initial agent. The choice between oral and nasal antihistamine should be decided based on patient preferences since efficacy appears to be similar. Despite the range of medication options available, effectiveness is often modest [11], and one-third to two-thirds of children and adults have limited or no response [12]. Such cases should be considered for allergen immunotherapy.

Oral Antihistamines

H1 antihistamines, although only moderately effective, are most commonly [11] 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 regular use. These long-standing medications have proven efficacy in clinical trials for the relief of rhinorrhea, sneezing, nasal itching, and nasal discharge. Additionally, these agents ameliorate ocular itching and watery discharge in case of concomitant allergic conjunctivitis. It should be noted that 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. However, the use of first-generation agents is limited by their anticholinergic (muscarinic receptors) adverse effects such as drowsiness and dry mouth. Mucosal dryness even in the nasal passages can be marked at higher doses. Sedation can affect the ability to drive safely or work in high-risk situations such as at industrial sites. Even without the subjective perception of drowsiness, the level of performance can be impaired. Cognitive impairment and other adverse effects are most significant among the elderly.

Topical Nasal 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.

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.

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Topical Nasal Decongestants

Topical decongestants such as oxymetazoline nasal sprays are modestly 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.

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 [13].

Adverse effects of intranasal corticosteroids include nasal dryness and epistaxis. There appear to be no long-term effects on nasal mucosa, hypothalamic-pituitary axis, bone growth in children, and the ocular lens [3].

Oral Antileukotrienes

Oral leukotriene receptor antagonists such as montelukast are not recommended as the primary treatment choice in allergic rhinitis due to limited efficacy [3]. Among patients with coexisting asthma, these agents may be justified in case of good clinical response. Leukotriene inhibitors show enhanced efficacy in allergic rhinitis when coadministered with an oral antihistamine.

Immunotherapy

Allergen-specific immunotherapy consists of subcutaneous or sublingual exposure to gradually increasing doses of one or more antigens over 3–5 years. This form of therapy is generally effective, and the effects last even after completion of the treatment. Apart from the inconvenience of twice-weekly injections, there is a rare chance of allergic reaction including anaphylaxis with subcutaneous treatment. The sublingual route appears to be safer and easier for patients as therapy can be administered at home [14]. Along with benefits of improvement in comorbid asthma and allergic conjunctivitis, new onset asthma and the development of other allergies are prevented by this modality.

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 inferior turbinate reduction surgery may be helpful. Acupuncture may be considered in selected patients based on patient preference.

Counseling and Patient Education

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.

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Prevention

There is insufficient evidence for or against the use of nasal rinsing [15], wearing a face mask outdoors, staying indoors especially 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, and keeping windows closed during pollen season, although some patients find these helpful based on anecdotal experience. Relocating to other areas during high pollen seasons may not be a feasible option for many patients.

The use of impermeable mattress covers from birth onward does not prevent sensitization to dust mites in infants. Unfortunately, breastfeeding has not been shown reduce the incidence of allergic rhinitis in prospective studies.

Family and Community Issues

Awareness campaigns about allergic rhinitis in most communities appears 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 and Anaphylactoid Reactions

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Definition/Background

Anaphylaxis is an acute, potentially life-threatening, multisystem syndrome that is characterized by the release of mast cell- and basophil-derived mediators into the circulation after exposure to an antigen [1]. Traditionally, anaphylaxis was used to describe immunoglobulin E (IgE)-mediated reactions while "anaphylactoid" was used to describe non-IgE-mediated reactions. Anaphylaxis and anaphylactoid reactions are clinically indistinguishable and the World Allergy Organization recently suggested that "anaphylactoid reaction" be eliminated, with anaphylaxis divided into immunologic and non-immunologic reactions [2].

The diagnosis of anaphylaxis is made clinically and can be based on three clinical scenarios that were identified via consensus at the National Institutes of Health in 2006: [1]

1. Acute skin or mucosal reaction *and at least one of the following*:
   (a) Respiratory compromise
   (b) Reduced blood pressure or symptoms of end-organ dysfunction
2. Two or more of the following that occur rapidly after exposure to a likely allergen:
   (a) Skin/mucosal involvement
   (b) Respiratory compromise
   (c) Reduced blood pressure
   (d) Gastrointestinal symptoms
3. Reduced blood pressure after exposure to a known allergen

Using data from the number of prescriptions for automatic epinephrine injectors, investigators have estimated that the prevalence of anaphylaxis is close to 2 % of the general population [3]. Recent studies also suggest that the prevalence is rising, most notably in younger age groups [4].

Potential triggers of anaphylaxis can include, but are not limited to, food, latex, insect stings and bites, medications (most commonly beta-lactam antibiotics and NSAIDs), immunotherapy, and physical factors such as UV light, cold, or exercise [5]. The more rapidly anaphylaxis develops, the more likely the reaction is to be severe and potentially life threatening [5]. Prompt recognition of signs and symptoms of anaphylaxis is critical, and epinephrine should be administered as soon as anaphylaxis is suspected [1].

History

The diagnosis of anaphylaxis is generally based on history and physical examination. A thorough yet efficient history is imperative to timely diagnosis. The provider should inquire about all exposures in the

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6 h prior to onset in order to identify possible causative agents [5]. This should include anything ingested in the prior 6 h, any insect sting or bite, any relation to exercise, the location of the event, and whether the event was related to heat or cold exposure. In children, foods most commonly cause anaphylaxis, whereas in adults, instigating agents may include drugs, foods, venom from stings or bites, exercise, and latex [6–8]. Any treatment that was implemented at the onset of symptoms should also be noted. Certain patient groups, including infants, teenagers, pregnant women, and the elderly, are at higher risk for more serious reactions [9, 10]. Other risk factors for severe reactions include poorly controlled asthma, concurrent use of certain medications (e.g., beta-blockers), and cardiovascular disease [9, 10].

Physical Exam

Initial evaluation should focus on patient stability and vital sign assessment. The remainder of the physical exam should focus on potentially involved organ systems, including lung auscultation, cardiac auscultation, tissue perfusion assessment, abdominal exam, skin exam, cognitive assessment, and inspection of the throat and mucus membranes. The most common physical exam finding is cutaneous urticaria and/or angioedema. Although significantly less common in children, cutaneous symptoms may be noted in 85–90 % of adult patients with anaphylaxis [5, 11, 12]. Physical examination findings are delineated in Fig. 1.

Ancillary Studies

Anaphylaxis should be diagnosed in a timely fashion, with history and physical being the primary mode of diagnosis. If suspected, empiric therapy should be initiated immediately, without waiting for ancillary testing results. Blood tests, such as tryptase levels, allergen serology, and blood counts, can be utilized by providers who are appropriately trained in their interpretation.

Differential Diagnosis

The differential diagnosis is broad, given the range of symptoms and severity that may occur. Anaphylaxis presentation may vary from mild urticarial rash to anaphylactic shock. Table 1 summarizes the differential diagnoses to consider in a patient with signs and symptoms of anaphylaxis [5].

Anaphylactic Triggers

Anaphylactic triggers can provoke a response through IgE-dependent and IgE-independent mechanisms (see Fig. 1).

Food

Food is the most common cause of anaphylaxis in the outpatient setting and accounts for 30 % of all fatal cases. Foods most commonly responsible for anaphylaxis include peanuts, tree nuts, shellfish, fish, cow's milk, soy, and egg. Asthma is a significant risk factor for more severe reactions related to food [5]. Special care must be taken by patients, parents, and caretakers to investigate the ingredients and contents of foods

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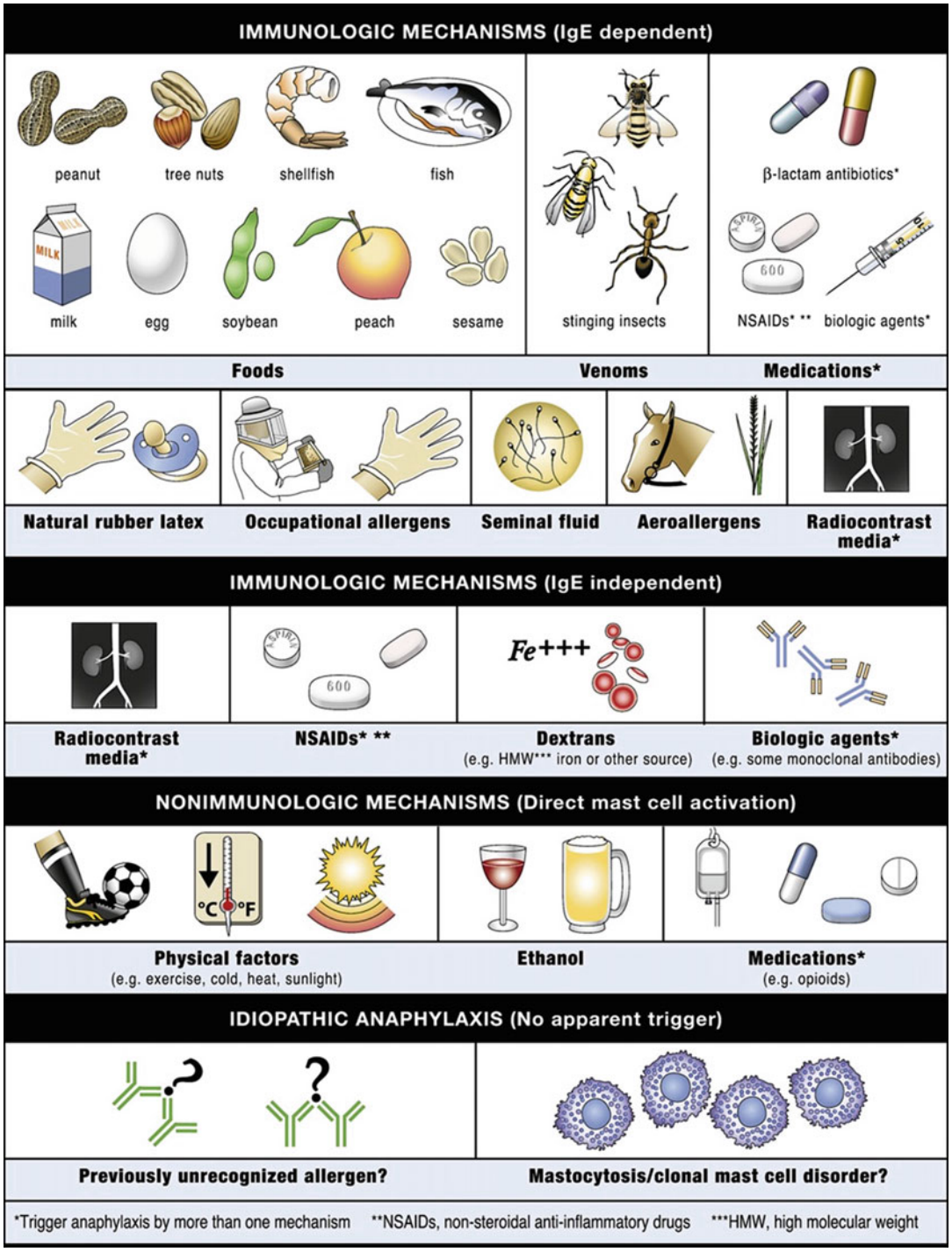

Fig. 1 Anaphylaxis mechanisms and triggers. Anaphylaxis typically occurs through an IgE-dependent immunologic mechanism, most commonly triggered by foods, stinging insect venoms, or medications. Medications can also trigger anaphylaxis through an IgE-independent immunologic mechanism and through direct mast cell activation. Radiocontrast media can trigger anaphylaxis through both IgE-dependent and IgE-independent mechanisms. Anaphylaxis triggered by seminal fluid or inhalant allergens is rare, and likely involves some systemic absorption of the allergen. In patients with idiopathic anaphylaxis, the possibility of a novel allergen trigger or of underlying mastocytosis or a clonal mast cell disorder should be considered. (Adapted with permission from Elsevier [10])

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Table 1 Differential diagnosis of anaphylaxis

Common diagnostic dilemmas	**Flush syndromes**
Acute asthma[a]	Perimenopause
Syncope (faint)	Carcinoid syndrome
Anxiety/panic attack	Autonomic 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
Neurologic events (seizure, cerebrovascular event)	Hyperventilation
Postprandial syndromes	Psychosomatic episode
Scombroidosis[b]	**Shock**
Pollen-food allergy syndrome[c]	Hypovolemic
Monosodium glutamate	Cardiogenic
Sulfites	Distributive[d]
Food poisoning	Septic
Excess endogenous histamine	**Others**
Mastocytosis/clonal mast cell disorders[e]	Nonallergic angioedema
Basophilic leukemia	Hereditary angioedema types I, II, and III
	ACE inhibitor-associated angioedema
	Systemic capillary leak syndrome
	Red man syndrome (vancomycin)
	Pheochromocytoma (paradoxical response)

Adapted with permission from Elsevier [10]

[a]Acute asthma symptoms, acute generalized urticaria, or myocardial infarction symptoms can also occur *during* an anaphylactic episode

[b]Histamine poisoning from fish, e.g., 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

to prevent trigger-food ingestion by a patient with a known food allergy. While laborious and at times tedious, this avoidance strategy is the cornerstone of prevention with regard to food-induced anaphylaxis.

Latex

There are three specific groups of people who are considered high risk for allergic reactions to latex: healthcare workers, children with spina bifida and genitourinary abnormalities, and workers with occupational exposure to latex. Patients with spina bifida and those with a positive history of latex allergy should have all procedures performed in a latex-safe environment. When possible, powder-free latex gloves and non-latex gloves should be considered to minimize latex sensitization [5].

Anesthesia

The incidence of anaphylaxis during anesthesia has been reported to range from 1 in 4,000 to 1 in 25,000 [5]. Potential offending agents can include neuromuscular blocking agents, opioids, antibiotics, blood products, or other perioperative agents. Once recognized, these reactions are managed similarly to anaphylaxis in other situations [5].

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Exercise

Rarely, in some individuals, exercise is the immediate trigger for anaphylaxis. These individuals often report ingestion of specific trigger foods or medications prior to exercise. The diagnosis is typically based on history, and treatment includes avoidance of trigger foods or medications prior to exercising, exercising with a partner, carrying auto-injectable epinephrine while exercising, and stopping exercise at the onset of symptoms. Prophylactic medications are not effective in preventing attacks in the majority of patients [5].

Insect Sting

Anaphylactic reactions to insect stings occur in 0.6 % of children and 3 % of adults [13]. These insects include wasps, honeybees, hornets, yellow jackets, and fire ants. In those adults with a prior large local reaction to an insect sting, the risk of anaphylaxis with subsequent stings is 5–10 %. In those who have already had an anaphylactic reaction to an insect sting, the recurrence rates vary between 25 % and 70 % [5]. Because treatment with venom immunotherapy is 90–98 % effective in preventing further anaphylactic reactions, consideration for allergy referral should be made in all patients who present with an anaphylactic reaction to an insect sting [5]. In addition to allergy referral, patients should be counseled on insect avoidance measures and given auto-injectable epinephrine with instructions on its proper use.

Other Medications

Penicillin is the most common cause of drug-induced anaphylaxis. In patients who are proven to have penicillin allergy by skin testing, 4 % will react to a cephalosporin challenge [5]. Penicillin allergy is self-reported in 5–10 % of all patients, although as many as 85 % of these individuals will not react to penicillin skin testing and can tolerate this class of agents [14]. Referral to allergy for evaluation and possible skin testing should be considered for select patients at risk for serious reactions or when the suspected antigen is unclear.

Vaccines

The rate of anaphylaxis following vaccine administration has been reported to be less than one per one million doses [15]. Outpatient settings where vaccines are administered should be equipped with necessary training and equipment to treat an anaphylactic reaction.

Idiopathic Anaphylaxis

The diagnosis of idiopathic anaphylaxis is made when extensive evaluation, including a detailed history of exposures, fails to identify a trigger. The symptoms and treatment of idiopathic anaphylaxis are the same as those with an identified trigger. Glucocorticoids and histamine-1 (H1) antagonists have been shown to reduce the frequency and severity of episodes in these patients [5]. Patients with idiopathic anaphylaxis should be considered for allergy referral.

Primary Treatment

All anaphylactic reactions should be treated emergently, regardless of presenting severity, as symptoms may rapidly progress. A study of fatal episodes of anaphylaxis demonstrated respiratory and cardiac arrest occurred with a median time of 30 min for food reactions, while iatrogenic triggers had a median time of arrest of only 5 min [16]. Because of the unpredictable nature of reactions, a prompt and systematic approach must be consistently employed. Before any actions are taken, it is essential to remove any

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precipitating factors. An initial survey to assess airway, breathing, circulation, and consciousness (ABCs) should always be performed.

Epinephrine should be administered as soon as the diagnosis of anaphylaxis is suspected [5]. The preferred dose of epinephrine (1:1000) is 0.2–0.5 mL (mg) and the pediatric dose is 0.01 mg/kg, delivered intramuscularly (IM). Intramuscular thigh injections in the lateral thigh have been shown to achieve the fastest plasma concentrations. Therefore, the vastus lateralis (lateral thigh) is the preferred location. This dose may be repeated every 5–10 min until symptoms resolve. Delayed treatment may increase mortality.

To help combat hemodynamic instability, patients should be placed in a supine position with the lower extremities elevated to limit the amount of peripheral blood distribution [5]. Supplemental oxygen should also be initiated immediately and oxygenation monitored continuously with pulse oximetry. Once intravenous (IV) access is obtained, fluid resuscitation should be started with 1–2 l of normal saline (NS). If bronchospasm is present after administration of epinephrine, inhaled short-acting beta-2 agonists can be given. Antihistamines may be administered as an adjunct to epinephrine for supportive care, but should not be given in place of epinephrine when anaphylaxis is suspected. While there is no direct outcome data for their use in anaphylaxis, antihistamines may mitigate cutaneous and cardiovascular complications [17, 18]. Conversely, glucocorticoids confer no benefit in the acute care of anaphylaxis but may prevent a biphasic response [5].

In the event that patients remain unstable following initial treatment measures, certain steps should be taken. Respiratory interventions should be escalated in a stepwise fashion. Providers should establish a low threshold for endotracheal intubation and cricothyroidotomy given the risk of airway obstruction, but only if adequately trained personnel are available to perform these procedures.

Secondary Treatment

Once patients are stabilized from acute anaphylaxis, patients should be observed for signs of biphasic anaphylactic reactions. Biphasic reactions, defined as a recurrence of symptoms after previous signs and symptoms of anaphylaxis have resolved, occur in 1–23 % of patients and are more common with food-induced anaphylaxis. Most biphasic reactions occur within 8 h after resolution of initial anaphylaxis, but may take up to 72 h to present [19]. Therefore, recommended observation time for anaphylactic patients is 6–12 h, with longer periods for suspected food-related anaphylaxis. Regardless of severity, all patients presenting with anaphylaxis should be educated and sent home with auto-injectable epinephrine and referral to an allergist considered.

Prevention

The most important strategy to prevent recurrent anaphylaxis is patient education. The foundation of prevention is avoidance of triggers. Some triggers, like stings or agents required for medical procedures, cannot be avoided. Thankfully, pharmacologic prophylaxis and immunotherapy can be used to diminish the risk of resultant significant reactions.

Pharmacologic prophylaxis is frequently utilized before administration of radiographic contrast media (RCM). Given the widespread use of contrast-aided radiographic imaging in the USA (greater than ten million exams annually), prophylactic measures should be employed when the benefit of imaging outweighs the risk of an allergic reaction. The best supporting evidence involves the use of diphenhydramine and/or prednisone. A systematic review of randomized trials involving the two medications demonstrated a decrease in cutaneous and respiratory symptoms following contrast administration

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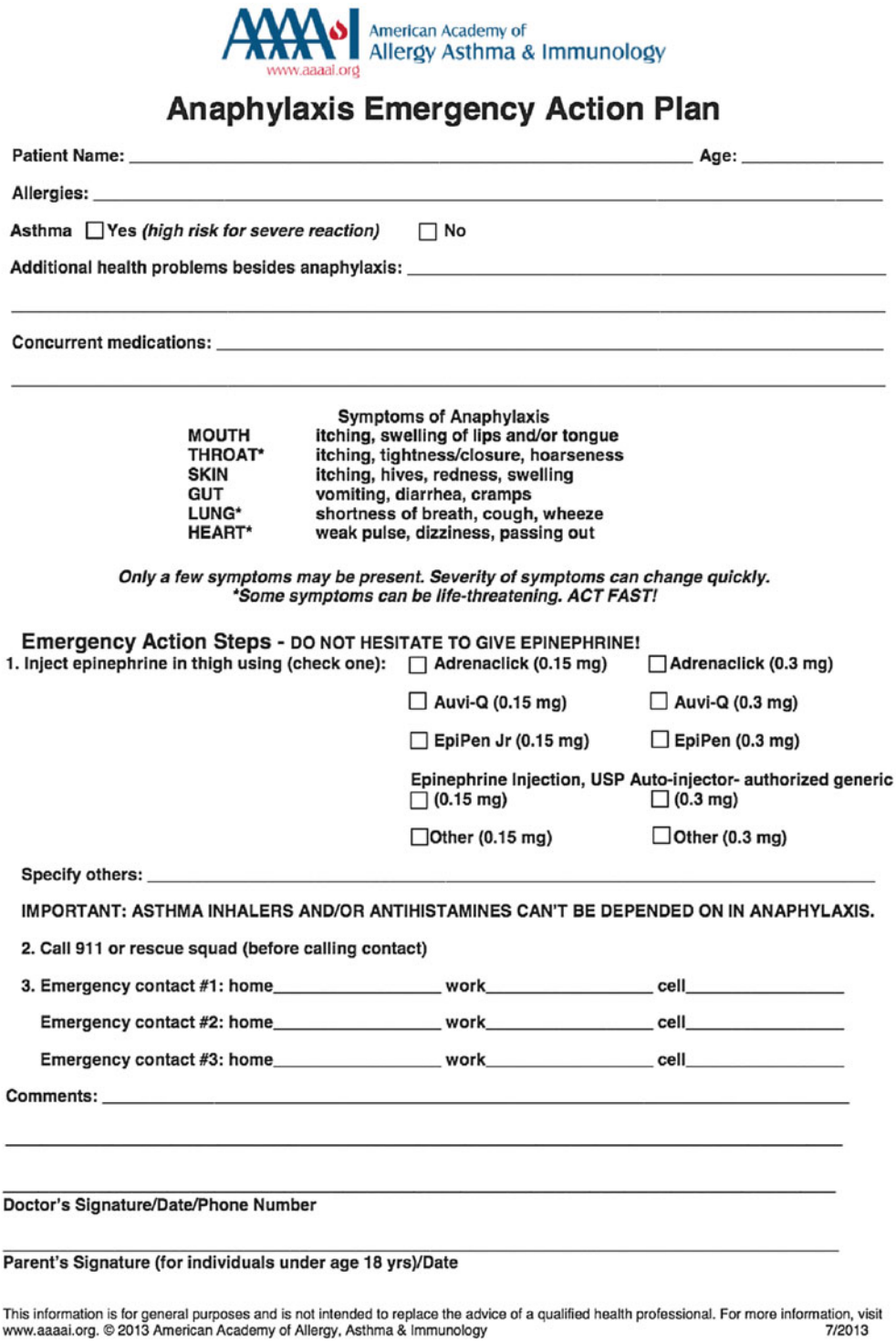

American Academy of Allergy Asthma & Immunology
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Anaphylaxis Emergency Action Plan

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. © 2013 American Academy of Allergy, Asthma & Immunology 7/2013

Fig. 2 Anaphylaxis Emergency Action Plan (Adapted with permission from the American Academy of Allergy, Asthma & Immunology and available online at https://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Libraries/Anaphylaxis-Emergency-Action-Plan.pdf)

[20]. While treatment regimens may vary, a common approach involves pretreatment with oral prednisone 50 mg at 13, 7, and 1 h(s) prior to a procedure in combination with oral, IM, or IV diphenhydramine 1 h prior to the procedure [21].

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Immunotherapy is another method that may minimize the risk of anaphylaxis with known triggers. It consists of repeated exposure to a particular allergen (or component of an allergen) to blunt the immune system's response. In the case of venomous insect stings, immunotherapy is 90–98 % effective in preventing systemic allergic reactions [5]. Consideration for referral to an allergist should be given for any patient with a previous systemic allergic reaction to an insect sting. Venom immunotherapy provides long-term protection and can potentially be terminated after 5 years with less than a 10 % risk of a subsequent severe reaction. However, indefinite venom immunotherapy may be appropriate in some clinical scenarios (i.e., near-fatal systemic reaction). Although the risk of a life-threatening adverse response to immunotherapy is very small, it should be performed only by professionals well trained in recognizing and treating anaphylaxis, in a setting with appropriate resources and equipment.

If the trigger is unknown, coordinated care with an allergist or immunologist is paramount. Regardless of the etiology, prevention should focus on early recognition, treatment with self-administered epinephrine, awareness of cross-reactivity, hidden allergies, risk of medical procedures, and overall risk of future anaphylaxis [22]. An epinephrine auto-injector should always be provided with instruction on appropriate use after an episode of acute anaphylaxis. A recent study demonstrated a concerning knowledge deficit in the use of auto-injectable epinephrine among both patients and general practitioners [23]. Additionally, 19 % of children who were treated with auto-injectors received no epinephrine intramuscularly [24].

Preparedness is the final component to prevention. A concerted effort should be made to inform others at home, school, work, etc. about an individual's tendency for anaphylaxis. Medical bracelets or information sheets with emergency phone numbers are available options. In addition, a comprehensive anaphylaxis emergency action plan is made available by the American Academy of Allergy, Asthma & Immunology (AAAAI) and should be provided to all patients who present with an episode of anaphylaxis (Fig. 2).

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Epstein-Barr Virus Infection and Infectious Mononucleosis

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General Principles

Background

The Epstein-Barr virus (EBV) is a double-stranded linear DNA virus. Its DNA core is enclosed by an icosahedral nucleocapsid and by a viral envelope. As a member of the Herpesviridae family, EBV is specifically a gamma herpesvirus [1]. There are two subtypes of EBV, EBV-1 and EBV-2, sometimes referred to as EBV types A and B. These are genetically very similar and are not often distinguished from each other in clinical practice [2].

One of the defining characteristics of the gamma herpesvirus class is its infection of and latency within lymphoid tissue. EBV primarily infects B lymphocytes, integrating itself into the genome and remaining latent. It can also infect natural killer (NK) cells and T lymphocytes, though with less efficiency [1–3]. It is the cause of heterophile-positive infectious mononucleosis, often referred to simply as "infectious mononucleosis" (IM). Colloquial names for it include "mono" and "the kissing disease," due to its primary method of transmission. EBV was the first virus discovered to contribute to the development of several types of malignancies in humans [4].

Epidemiology

Although greater than 90 % of the world's population has antibodies to EBV, the clinical course and significance of EBV varies significantly between developing and industrialized countries. In developing countries, as well as members of lower socioeconomic status living in industrialized countries, there is extensive transmission of the virus in infancy and early childhood; the majority of children develop antibodies by the age of three and do not typically experience symptomatic infection. In the industrialized world, EBV typically causes IM primarily among adolescents and young adults, with estimates of yearly incidence ranging from 100 to 500 per 100,000 adolescents in the United States [2, 5]. Worldwide the incidence is 20–70 per 100,000 annually. Adults over the age of 30–40 are less frequently symptomatic; when symptoms in this age group occur, it is often among those suffering from immune deficiency states such as AIDS.

Clinical Presentation

EBV has an incubation period of approximately 30–50 days. The prodromal phase is characterized by the insidious onset of symptoms that include fatigue, malaise, and myalgia, typically lasting 1–2 weeks. Fever may or may not occur during this time and may last more than a month [2]. Sore throat, lymphadenopathy, and the typical prodromal symptoms form the classic triad of IM, occurring in over 80 % of patients [3]. The pattern of lymphadenopathy is generalized, present in 90 % of patients, and may include epitrochlear adenopathy.

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Table 1 Factors increasing likelihood of IM

Pharyngitis with abnormal liver enzymes
Atypical lymphocytosis >10 % (specificity 92 %)
Lymphocytosis >50 % (specificity 85 %)
Palatal petechiae
Splenomegaly
Posterior cervical lymphadenopathy

Additional signs include splenomegaly in over 50 %, petechiae present at the junction of the hard and soft palate, tonsillar exudates, hepatomegaly, and a maculopapular rash which may last anywhere from 15 to 50 days. Also typical of IM is the eruption of a copper-colored maculopapular rash specifically in response to amoxicillin, which may have been given for presumptive strep throat. In adults, signs such as fever, transaminitis, hepatomegaly, or pneumonitis may be more common than the lymphadenopathy and pharyngitis typical of adolescent cases [6]. Table 1 summarizes the symptoms whose presence increases the likelihood of a diagnosis of IM.

Symptoms, particularly malaise and fatigue, may last for months. Rarely, patients may develop chronic active EBV infection (CAEBV). This condition is defined by the presence of symptoms accompanied by markedly elevated titers of EBV antibody, indicating active replication that persists for more than 6 months. Guidelines were proposed in 2005 for the diagnosis of CAEBV, including (1) persistent or recurrent IM-like symptoms; (2) unusual pattern of anti-EBV antibodies, specifically IgG against EBV VCA (greater than 1:640) and early antigen (greater than 1:160), and/or detection of EBV DNA in affected tissues, including blood; and (3) no other known disease process present to explain chronic illness at diagnosis [7].

Diagnosis

The clinical diagnosis of IM most commonly relies on the presence of typical symptoms in the presence of a positive heterophile antibody test ("monospot") [8, 9]. The complete blood count (CBC) often reveals 20 % or greater atypical lymphocytes; the white count may be normal or mildly elevated [2]. Lymphocytosis is more likely to be seen in older patients [6].

In certain instances, the heterophile antibody test can be falsely negative. In children under the age of 12, the test may be positive in only 25–50 % of patients. The test is particularly insensitive in those below 2 years of age. It may also be negative in up to 25 % of patients during the first week of infection, as well as 5–10 % of patients in or after the second week [2]. Infections such as toxoplasmosis and cytomegalovirus may cause false-positive heterophile antibody tests. Furthermore, antibodies may persist for 1 year or more. However, when positive in the presence of IM symptoms, test sensitivity is approximately 85 % and specificity approaches 94 % [3]. If EBV is strongly suspected but heterophile antibody testing is negative, EBV-specific antibodies can be obtained for confirmation of infection.

Differential Diagnosis

Table 2 summarizes the differential diagnosis of IM caused by EBV. It can be difficult to distinguish between disease entities clinically, particularly toxoplasmosis and cytomegalovirus (CMV). In high-risk populations, such as pregnant patients, it is prudent to pursue confirmatory testing due to the risk of TORCH infections to the fetus.

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Table 2 Differential diagnosis for infectious mononucleosis

Diagnosis	Differentiating characteristics
Cytomegalovirus, toxoplasmosis	Can be clinically indistinguishable
	Usually heterophile antibody negative
	Clinical suspicion requires further testing in pregnant women due to risk of congenital infection
HIV	Weight loss, mucocutaneous ulceration, rash 48–72 h following fever
	Concurrent symptomatic infection from EBV more likely in adults with HIV/AIDS
	Presence of oral hairy leukoplakia (OHL) is specific for HIV
Streptococcal pharyngitis	Exudative pharyngitis, positive rapid strep or throat culture
	More typically anterior cervical lymphadenopathy than posterior
Adenovirus	Heterophile negative
	Less systemic lymphadenopathy
Viral hepatitis	Jaundice is more common, particularly in hepatitis B
	More common among middle-aged adults than EBV
Rubella	Presence of pink maculopapular rash that begins on the face then spreads to the body
	Clinical suspicion requires further testing in pregnant women due to risk of congenital infection
Leukemia	Very high or very low white blood cell count
	Hemolytic anemia
	Moderate to severe thrombocytopenia
Drug effect	Phenytoin, carbamazepine, isoniazid, minocycline

Streptococcal pharyngitis can usually be distinguished by the presence of exudative pharyngitis, as this is more common in strep pharyngitis than in IM; it can, however, still occur in IM. Cervical adenopathy commonly involves the posterior cervical chain and may be generalized, as opposed to streptococcal pharyngitis, which tends to cause anterior cervical adenopathy [2, 4]. These two are best distinguished from each other by a rapid test for streptococcal antigen and/or throat culture.

Laboratory findings more suggestive of EBV include atypical lymphocytosis greater than 20 % and lymphocytosis of greater than 50 %. Not uncommonly, EBV infection may result in hematologic abnormalities such as hemolytic anemias or cytopenias. Similar findings may be seen in leukemia.

Complications

During the acute infection, the most worrisome complications include hemolytic anemia, encephalitis, meningitis, Guillain-Barré syndrome, myocarditis, pneumonitis, and acute interstitial nephritis. Airway compromise from pharyngitis or tonsillitis is rare but may be life threatening [2, 3, 5]. Finally, although rare, the risk of splenic rupture is greatest in the first 21 days after infection. This becomes an important consideration for return-to-play guidelines for athletes as well as military trainees, who often fall within the age range for EBV infection (see Community and Family Considerations).

In terms of long-term complications, lymphoproliferative disorders and other malignancies are of concern, particularly among immunocompromised individuals. Impaired immunity presumably allows increased viral replication over time, enhancing the ability of EBV to transform cells. While the complications of infection tend to affect the B-cell line, they remain varied and have the potential to affect almost every system. For example, nasopharyngeal carcinoma, particularly the undifferentiated type, is prevalent in Southern China, among Caucasians in North Africa, and the Inuit of North America [2].

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EBV-related thymic cancer has been identified in the United States, as well as leiomyosarcoma, Burkitt lymphoma, and other B-cell lymphomas. Oral hairy leukoplakia is a manifestation of EBV replication and can be seen in adults with HIV/AIDS. Children with AIDS can develop lymphoid interstitial pneumonitis, leading to dyspnea and respiratory distress [2, 3, 6, 10].

Evidence exists that suggests an association between EBV and the development of multiple sclerosis [11–13]. However, the exact relationship remains to be elucidated. It is likely multifactorial, to include age at infection and genetic susceptibility or predisposition. Lingering fatigue can also be a complication of IM, creating implications for the patient's subsequent ability to participate in school, work, and play. Females are particularly affected [14, 15]. It is important to note that to date no evidence exists to link infectious mononucleosis with chronic fatigue syndrome. Chronic active EBV infection is distinct from chronic fatigue syndrome.

Additionally, there exists evidence linking psychologically stressful events within the 6 months prior to infection with the severity of EBV infection symptoms and subsequent time to recovery [14]. A systematic review of the literature showed that while premorbid psychological diagnoses did not seem to correlate with length of illness or failure to recover, female sex and older age both appeared to contribute to prolonged time to recovery and distress following the active phase of illness. Furthermore, poor physical conditioning, lower physical functioning, and longer absence from work or school were consistently associated with prolonged illness [16].

Management

Supportive care is the mainstay of treatment for infectious mononucleosis. Acyclovir, while effective in reducing replication rate of the virus and oral shedding, does not alter the disease length or severity of symptoms [17]. NSAIDs, oral hydration, and salt water gargles may help provide symptomatic relief. Bed rest can be offered to those with especially severe fatigue, though evidence suggests that this may hinder recovery.

Tonsillar enlargement causing difficulty breathing may be treated by hydration, humidified air, a short course of corticosteroids, and elevation of the head of the bed. Suggested dosing of steroids is prednisolone one milligram per kilogram orally for 7 days with subsequent tapering over 7 days [2]. Significant swelling with respiratory compromise may necessitate intubation and/or tonsillectomy. Corticosteroids can also be considered in cases of thrombocytopenia with bleeding, autoimmune hemolytic anemia, seizures, and meningitis. Corticosteroids should not be used in uncomplicated cases of EBV [2, 3, 6].

Prevention

Symptoms may not present until weeks after the initial inoculation. Thus, prevention of transmission can be difficult. Advice against kissing children on the mouth due to the intermittent asymptomatic oral shedding of the virus would seem to be a sensible intervention. Toys, particularly in daycare settings, should be kept clean to prevent transmission by fomites.

Furthermore, although transmission through sexual contact has been reported, it has not been associated with development of clinically significant disease. Studies have demonstrated the coexistence of EBV with the human papilloma virus (HPV) in cervical neoplasms [18]. There has not been, however, an established link to the development of cervical cancer.

Vaccines against EBV are currently being studied. However its clinical application is likely to be for the prevention of complications, specifically malignancies, rather than reducing rates of primary infection [2].

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Family and Community Issues

For active patients, including athletes and those serving in the military, activity restriction can help protect against splenic injury or rupture, given the prevalence of splenomegaly in IM. There are no conclusive studies that establish firm guidelines regarding return to play for athletes recovering from IM. Recommendations vary, but include restriction from contact sports and high-risk activities for four weeks from symptom onset. Light activity may be resumed if the patient is afebrile and hydrated and has no spleen or liver enlargement. Complete return to play should be considered only if the patient feels well, as malaise and fatigue can persist for months after the infection resolves [2, 3, 5, 19, 20].

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Viral Infections of the Respiratory Tract

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General Principles

Definition/Background

Viral infections of the respiratory tract are common events in all age groups and are the leading cause of mortality in children under 5 years of age in developing countries [1]. These infections cause significant economic burden, with estimated direct and indirect medical costs in the US exceeding $70 billion annually [2, 3]. Children under the age of 5 have an average incidence rate of four to six viral respiratory infections/year and the rate gradually decreases to one to two/year in most adults [4].

Epidemiology

Respiratory viruses spread mainly through direct contact with infected individuals, predominantly through respiratory droplets. While respiratory infections tend to be present throughout the year in warmer areas, in temperate climates these are seen most often in the winter months (see Fig. 1) [5] Although some of the new and emergent infections may arise from an animal host, the majority of the respiratory viral infections are spread from other humans. Most of the illnesses are introduced to families by young, school-age children or other caregivers with secondary infections occurring following these initial cases.

Pathophysiology

Respiratory infections caused by viruses are transmitted primarily by droplets. These viruses can attach to the upper or lower respiratory tract and induce an IgA-mediated immune response in the mucous secretions of the respiratory tract and an IgG-mediated response in serum. Respiratory viral infections generally induce adaptive immune responses that should be protective. However, repeated respiratory infections are due to the large numbers of serotypes of each virus, or antigenic variations in viruses such as the influenza virus, and their ability to induce similar, non-specific clinical signs.

The clinical presentation of respiratory viruses can vary, however their clinical symptoms are often very similar. Table 1 describes common clinical presentations and the viruses that cause these [4, 6–8].

Laboratory Testing

Respiratory viruses may be identified using viral cultures or by rapid tests identify antibodies to the virus [9]. Viral cultures are reserved primarily for research purposes given the time for culture growth, the cost, and often their relatively low sensitivity. Clinical diagnosis of respiratory viral infections remains the standard in clinical practice. Rapid tests are being used more frequently in the clinical setting to identify influenza and RSV infections and initiate targeted treatments, however rapid virus detection does not reduce antibiotic use or cost [10].

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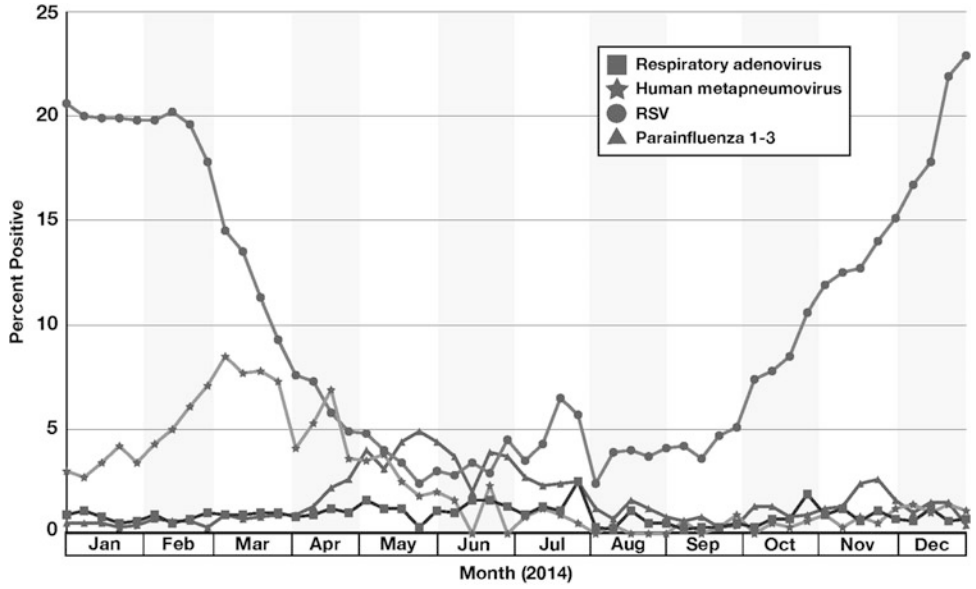

Fig. 1 Weekly laboratory test data of respiratory viruses in the USA, 2014 (Data from CDC National Respiratory and Enteric Virus Surveillance System. http://www.cdc.gov/surveillance/nrevss/)

Table 1 Clinical presentations and causes of viral respiratory syndromes [4, 6–8]

Clinical condition	Common causes	Occasional causes	Infrequent causes
Common cold	Rhinovirus Coronavirus	RSV Influenza Parainfluenza	Metapneumoviruses Enteroviruses Adenovirus
Laryngitis	Parainfluenza Rhinovirus	Influenza	Adenovirus
Acute bronchitis	Influenza Adenovirus RSV	Parainfluenza Coronavirus Rhinovirus	Enterovirus Metapneumovirus
Influenza like illness[a]	Influenza A	Influenza B	Enterovirus Adenovirus
Croup	Parainfluenza	Influenza RSV	
Pneumonia	RSV Influenza	Adenovirus	Rhinovirus Coronavirus Herpes Simplex virus
Pharyngotonsillitis	Adenovirus Herpes Simplex Virus	Enterovirus Influenza B	
Bronchiolitis	RSV	Human metapneumovirus Influenza Parainfluenza	Bocavirus Coronavirus Adenovirus

[a]Influenza includes – fever, cough, myalgia and malaise

Laboratory tests are increasingly being used to differentiate viral from bacterial infections, since early use of antibiotics may be advantageous in the latter. C reactive protein (CRP) and procalcitonin levels in blood are two of the tests used. While procalcitonin-guided treatment algorithms have been shown to decrease antibiotic use [11], CRP is neither specific nor sensitive enough to differentiate a bacterial respiratory infection from one that is caused by a virus [12].

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Common Cold

Definition/Background

The common cold, an acute infection of the upper respiratory tract that is usually self-limited, is the most frequent human infection [13, 14]. There are over *one billion* colds every year in the United States, and it is estimated that the common cold results in 20 million days of absence from work and 22 million days of absence from school each year [14, 15]. Typical common cold symptoms consist of nasal congestion and discharge, sore throat, cough, sneezing, and sometimes headache, with symptoms usually lasting less than 10 days in duration. These symptoms are fairly nonspecific and can easily be confused with allergies or early symptoms of more serious diseases. However, taking a detailed history, particularly identifying sick contacts, is usually helpful in distinguishing the common cold from other illnesses.

Causes

Although numerous viruses have been identified as etiologies of the common cold (see table of viral prevalence by illness presentation), rhinoviruses are by far the most common viruses detected across all age groups in the setting of common cold symptoms, accounting for 30–50 % of all cases [4, 14, 16]. Coronaviruses account for 10–15 % of cold cases, and influenza viruses are detected 10–15 % of the time. Given that cold viruses such as respiratory syncytial virus also are responsible for many flu-like illnesses, there is significant overlap in viral etiologies of the common cold and flu syndromes [4, 14].

Clinical Manifestations

Rhinovirus infections typically begin with a sore throat, soon followed by nasal congestion, rhinorrhea, cough, and sneezing. As the illness progresses, sore throat symptoms tend to resolve quickly, and the initially watery rhinorrhea becomes increasingly purulent. Fever is uncommon among adults with colds, but is more frequent in children with viral respiratory infections. Common cold symptoms peak in severity within 2–3 days of onset, and have a mean duration of 7–10 days [14].

Diagnosis

The diagnosis of the common cold is primarily based on clinical symptoms alone, and is often correctly made by adult patients themselves. Diagnosis in children and infants can be more difficult, especially in the early course of a febrile illness. Streptococcal pharyngitis can resemble early common cold symptoms, but the nasal congestion and drainage usually seen in common cold are atypical in streptococcal pharyngitis [14, 16]. Given the wide range of overlap in symptoms caused by different respiratory viruses, influenza included, it is often impossible to identify a specific viral etiology for cold symptoms in a particular patient. Although rapid detection of viral pathogens with real-time polymerase chain reaction can increase diagnostic accuracy, it has not been shown to reduce antibiotic use or costs, and therefore is of limited use in everyday clinical practice [10].

Treatment

The approach to treatment for the common cold focuses on symptomatic relief as well as prevention. Antibiotics are ineffective and inappropriate treatment for the common cold and should be avoided in adults and children [17, 18]. Over the counter cough and cold medications should be avoided in all children younger than 4 years due to the potential for harm and lack of benefit. Products shown to improve cold symptoms in children include vapor rub, zinc sulfate, *Pelargonium sidoides* extract, and buckwheat honey, although the quality of the evidence varies. Ineffective treatments for children include both inhaled and oral corticosteroids and *Echinacea*. Among adults, decongestants, antihistamine/decongestant combinations, and intranasal ipratropium have been shown to improve cold symptoms [17, 18].

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Additionally, non-steroidal anti-inflammatory drugs have been shown to relieve discomfort due to colds but not to improve respiratory symptoms [19]. When taken within 24 h of symptom onset, zinc has been shown to reduce the duration of common cold symptoms in healthy adults [20]. *Echinacea* plant preparations have not proven effective in treating common colds among adults [21]. In supplementation trials, regular use of vitamin C did not decrease the incidence of common colds, but did have a positive effect on symptom duration and severity. Therapeutic trials of vitamin C during a cold have not shown a significant effect on common cold symptom reduction, but it may be worth considering in individual cases given its favorable safety profile and low cost [22].

Laryngitis

Definition/Background

Inflammation of the larynx can be caused by a variety of conditions, including: viral or bacterial infection, acid reflux, voice misuse and overuse, toxic inhalation or ingestion, postnasal drainage, or coughing from any cause. Acute laryngitis, defined as inflammation of the larynx or vocal cords lasting less than 3 weeks, is one of the most common disorders of the larynx. Symptoms include lowering of the normal pitch of the voice or hoarseness, usually lasting from 3 to 8 days. Other symptoms of an upper respiratory infection are common along with laryngitis, and the condition has been linked to changes in the weather [23].

Treatment

Although acute laryngitis is usually caused by a viral infection, there are no useful clinical criteria to distinguish between viral and bacterial causes such as *Moraxella catarrhalis*, *Haemophilus influenzae*, or *Streptococcus pneumoniae.* Viral laryngitis is likely caused by the same viruses as the common cold (i.e., rhinovirus, coronavirus). Treatment is largely supportive, and includes voice rest, corticosteroids, and proton pump inhibitors [24]. Antibiotics are often prescribed for acute laryngitis. However, a recent systematic review concluded that antibiotics are of no benefit in the treatment of acute laryngitis [23].

Influenza

Definition/Background

Influenza is an acute respiratory illness caused by the influenza virus. In temperate climates, seasonal epidemics of influenza occur annually during the winter months, while in tropical climates influenza cases occur intermittently throughout the year [24]. Worldwide, three to five million people develop influenza each year and approximately 250,000–500,000 die of influenza-related illness [25]. The Epidemiology and Prevention Branch in the Influenza Division at the Centers for Disease Control and Prevention (CDC) tracks and reports influenza activity in the United States in a weekly report throughout the influenza season [26]. In the USA, influenza can peak in the colder weather months with most peaks occurring in February (see Fig. 2) [28]. Influenza results in significant economic costs as well as morbidity and mortality. Between 1976 and 2007 in the USA, estimated deaths attributable to influenza ranged from 3,000 to 49,000 per year, with the majority of deaths occurring in those aged >65 years [28].

Causes

The influenza virus is a single stranded RNA virus from the Orthomyxoviridae family that comes in three subtypes: A, B, and C. Human influenza virus types A and B cause the epidemics of human disease, while influenza virus type C causes a mild respiratory illness similar to the common cold [29]. The influenza

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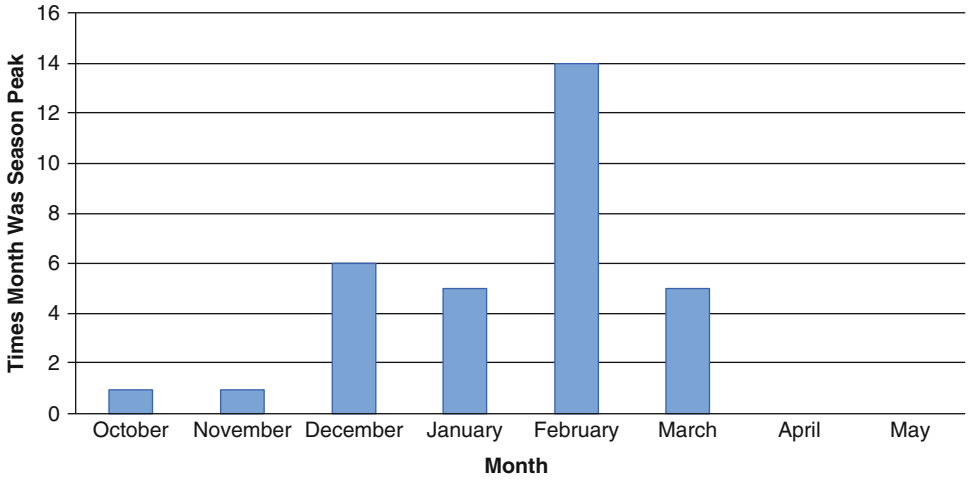

Fig. 2 Peak month of flu activity 1982–1983 through 2013–2014 [27]

A virus is further classified by the type of surface hemagglutinin (H) and neuraminidase (N) antigens that are expressed [30]. The appearance of new combinations of the H and N antigens results in "antigenic shifts" that have the potential to cause pandemics of human illness due to a lack of pre-existing immunity [29]. Within the last decade, two new strains of influenza A have emerged and resulted in pandemics- the H1N1 strain in Mexico in 2009 and the H7N9 strain in China in 2013 [31].

Prevention

Vaccination is the preferred public health method for prevention of influenza. Both inactivated influenza vaccine (IIV) and live attenuated influenza vaccine (LAIV) are available each season and are created from the circulating influenza A and B virus isolates that are anticipated to circulate in the following season according to recommendations of the World Health Organization [32]. Current recommendations call for annual influenza vaccination for all individuals greater than 6 months of age. The LAIV is recommended over the IIV for children ages 2–8 when immediately available if the child has no contraindications to the live attenuated vaccine. When vaccine supply is limited, preference should be given to those at higher risk, including children age 6–59 months, adults >50 years of age, those with immunosuppression or other severe chronic disease including morbid obesity, women who are or will become pregnant during the influenza season, residents of long-term care facilities, and Native Americans/Native Alaskans [32]. At this time, vaccination demonstrates a minimal effect on symptomatic influenza in otherwise healthy adults, with one case prevented for every 71 adults vaccinated [33]. However, universal vaccination is encouraged to improve herd immunity to influenza thus protecting high-risk individuals [34].

In certain situations, the antiviral medications oseltamivir or zanamivir can be used as an adjunct to vaccination for prevention of influenza. In a meta-analysis of prophylaxis trials, both medications demonstrated a significant reduction in the risk of symptomatic influenza in individuals and in households [35]. However, due to concern for increasing viral resistance, the CDC does not recommend the routine use of chemoprophylaxis for prevention of influenza, but rather recommends judicious use for those with known exposure who are at high risk for influenza complications or for whom the influenza vaccine is contraindicated [34].

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Clinical Manifestations

Infection of the respiratory tract by influenza virus classically results in acute onset of systemic and respiratory symptoms such as fever, cough, sore throat, nasal congestion, headache, myalgias, or malaise [32]. However, infection by influenza virus can be asymptomatic or cause other syndromes such as the common cold, pharyngitis, or pneumonia. Other viruses such as respiratory syncytial virus, adenovirus, or coronavirus can also cause an influenza-like illness [30]. The majority of those who get influenza will recover within 3–7 days, but cough and fatigue may persist beyond 2 weeks. Some develop complications such as pneumonia (either viral or a secondary bacterial infection), which can be life threatening, particularly for those at high risk. Influenza infection can also exacerbate other underlying chronic diseases such as asthma, COPD, and congestive heart failure.

Diagnosis

If influenza is suspected clinically and the patient would benefit from antiviral treatment (see below), a presumptive clinical diagnosis of influenza should be sought. Reverse transcriptase polymerase chain reaction (RT-PCR) is the most sensitive and specific method of influenza diagnosis according to the Infectious Disease Society of America, however the test is slow and can often take several days for a definitive result. Rapid influenza diagnostic tests (RIDTs) are antigen tests with results often available quickly enough to be clinically relevant. However, the results have poor sensitivity: in a meta-analysis of 159 studies of RIDT's compared to RT-PCR or viral culture, the RIDT's demonstrated a pooled sensitivity of 62.3 % (95 % CI 57.9–66.6 %) and a pooled specificity of 98.2 % (95 % CI 97.5–98.7 %) [36]. For this reason, a positive RIDT result can be considered adequate to make the diagnosis, but a negative RIDT result should not be used to exclude the diagnosis of influenza when clinically suspected.

Treatment

Four pharmacologic agents are available to treat influenza in the United States: the neuraminidase inhibitors zanamivir and oseltamivir, and the adamantanes amantadine and rimantadine. Amantadine and rimantadine are only effective against influenza A, and due to high rates of resistance (>99 % for influenza A H3N2 or H1N1) their use is not currently recommended [34]. Zanamivir (inhaled) and oseltamivir (oral) are effective against both influenza A and B and still demonstrate low rates of resistance [37]. Treatment with one of these agents is recommended as soon as possible for patients with known or suspected influenza who are hospitalized, manifest severe, complicated, or progressive illness, or are at high risk for complications, including adults >64 years of age, children <2 years of age, persons with severe underlying chronic illness or immunosuppression, or several other high risk groups (Table 2) [34]. One recent meta-analysis demonstrated small, non-specific effects on reducing the total duration of influenza symptoms without a demonstrated reduction in complications for otherwise healthy adults with influenza treated with oseltamivir or zanamivir [35]. The use of a neuraminidase inhibitor for treatment of proven or suspected influenza in an otherwise healthy adult without risk factors for severe disease should be determined by clinical judgment and shared decision making.

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 production. The symptoms of acute bronchitis can overlap with other clinical syndromes of upper and lower respiratory tract infections. Symptoms generally last for

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Table 2 Persons at high risk for complications from influenza [34]

Children aged <5 years (especially those aged <2 years)
Adults aged ≥65 years
Persons aged ≤18 years who are receiving long-term aspirin therapy
Individuals with chronic pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematologic (including sickle cell disease), metabolic disorders (including diabetes mellitus) or neurologic and neurodevelopment conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy (seizure disorders), stroke, intellectual disability (mental retardation), moderate to severe developmental delay, muscular dystrophy, or spinal cord injury)
Immunosuppressed individuals, including that caused by medications or by HIV infection
Pregnant or postpartum women (within 2 weeks after delivery)
American Indians/Alaska Natives
Morbidly obese individuals (i.e., BMI ≥40)
Nursing home, or other chronic-care facility residents

2 weeks, but the associated cough may persist for up to 8 weeks [38]. In the USA, acute bronchitis is the ninth most commonly encountered diagnosis in the outpatient setting [39].

Causes

The majority (>90 %) of cases of uncomplicated acute bronchitis are due to a viral infection [40]. Influenza A and B viruses, parainfluenza virus, respiratory syncytial virus, coronavirus, adenovirus, rhinovirus, and human metapneumovirus have all been identified, though in the majority of cases no causative agent is isolated [41]. *Bordetella pertussis*, *Mycoplasma pneumoniae*, and *Chlamydophila (Chlamydia) pneumonia* cause acute bronchitis in approximately 5–10 % of adult cases [40]. Though pneumonia-causing pathogens such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis* are sometimes isolated from patients with acute bronchitis, their role is unclear and they do not appear to be etiologic agents of bronchitis in otherwise healthy adults [40, 41].

Diagnosis

The diagnosis of acute bronchitis is based on clinical evidence of a lower respiratory tract infection with a cough persisting at least 5 days without evidence of pneumonia [41]. In the absence of abnormal vital signs or physical exam findings consistent with pneumonia, a chest radiograph is not necessary unless the patient is elderly or otherwise immune suppressed [41]. Other alternative diagnoses such as asthma, pharyngitis, sinusitis, influenza, and pertussis should be ruled out when clinically appropriate.

Treatment

Antibiotic treatment of acute uncomplicated bronchitis is not recommended [40]. Systematic reviews of the available evidence have demonstrated that, though there may be a modest reduction in duration of cough-related symptoms, this is unlikely to be clinically significant [38]. Overall there is no benefit to using antibiotics for acute bronchitis in otherwise healthy individuals, unless there is clinical suspicion for pertussis as the etiologic agent [40]. Clinical judgment should guide the determination of antibiotic use for those who are elderly or who have chronic respiratory comorbidities.

In spite of this recommendation, approximately two thirds of patients with acute bronchitis are prescribed antibiotics in the United States [42]. Procalcitonin-guided therapy has been shown to safely reduce antibiotic use in lower respiratory tract infections (including pneumonia, asthma, COPD, and uncomplicated acute bronchitis) in the primary care setting and can help guide treatment if bacterial infection is a concern [43].

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Special Populations: Children, Elderly, and the Immunocompromised

Children tend to have more episodes of respiratory infections than adults and, while many have 4–6 infections/year, 15 % of children may have up to 12 infections in a year. Children who attend daycare have a 50 % more respiratory infections than those who do not [44]. The majority of infections in children are self-limiting with supportive care the only treatment required.

Viral respiratory infections are particularly concerning in the elderly and the immunocompromised. Secondary infections including pneumonia and sepsis cause increased morbidity and mortality in these populations. All-cause mortality is also increased with influenza in this population [45]. Among the institutionalized elderly, respiratory syncytial virus (RSV), parainfluenza, and influenza are important causes of respiratory illness. Along with respiratory precautions and hand hygiene, increased efforts towards immunization of the elderly and their caregivers are important to decrease morbidity in this population.

New and Emergent Respiratory Infections

The ease of travel and the interdependency of markets have brought new challenges of spreading infectious pathogens. It is in this context that the practicing physician should be aware of the growing threats of emergent respiratory infections and their pandemic potential. Severe acute respiratory syndrome-coronavirus (SARS-CoV), avian influenza viruses H5N1, H7N9, and H10N8, swine-origin influenza A H1N1, human adenovirus-14, and the Middle East respiratory syndrome-coronavirus (MERS-CoV) are a few of the viruses that are concerning for relatively high mortality rates and the potential to result in pandemics [46]. Some of these are zoonotic, affect the lower respiratory tract, and have high morbidity and mortality rates. The most effective methods of preventing these emerging viruses at this time include the scrupulous adherence to respiratory precautions and an awareness of regional spread and outbreaks [32].

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 [47]. Currently, an effective vaccine is available only for influenza. Other measures of prevention include antivirals for close contacts of those with influenza and use of palivizumab, a monoclonal antibody, in high-risk individuals to prevent respiratory syncytial virus (RSV) infections.

Family and Community Issues

Antibiotic resistance in the healthcare setting is a growing threat to public health, and, as of 2013, two million people become infected and 23,000 people die each year from antibiotic-resistant infections [48]. 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. To avoid inappropriate use of antibiotics for viral

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infections, physicians should strive to adhere to clinical guidelines and decision-support tools combined with laboratory testing when indicated to determine risk for a bacterial infection.

Commonly, patients or parents will request antibiotics for viral infections, and physicians can feel pressured to prescribe antibiotics to address social stressors such as school or work absences. In this situation, family doctors need to clearly communicate that treating viral infections with antibiotics is ineffective and may be harmful. Additionally, pointing out negative or reassuring findings on exam and giving a specific diagnosis ("viral pharyngitis" or "viral upper respiratory infection" instead of "just a virus") can help with counseling patients. Lastly, it is important to acknowledge the suffering and discomfort caused by viral infections, to proactively offer treatment for symptoms, and to outline the normal course of the illness with clear indications for follow-up if symptoms do not resolve within an expected timeframe [49].

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Family Medicine
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Rhinosinusitis and Tonsillopharyngitis

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Rhinosinusitis

Sinusitis is characterized by mucosal inflammation of the sinuses which is almost always accompanied by inflammation of the nasal passages. Since nasal mucosa is contiguous with paranasal sinus mucosa, the term *sinusitis* is often used interchangeably with *rhinosinusitis* [1]; the latter term will be used in this chapter. Rhinosinusitis can be acute (less than 4 weeks' duration), subacute (4–12 weeks), or chronic (greater than 12 weeks) [2].

Epidemiology

Rhinosinusitis is extremely common; in a 2008 national survey, 1 in 7 adults reported having been diagnosed with rhinosinusitis in the previous 12 months [3]. The estimated prevalence of chronic rhinosinusitis in the USA ranges from 2 % to 16 % [4]. Women are disproportionally affected compared to men, and both acute and chronic rhinosinusitis are most prevalent in middle-aged adults compared to any other age group [3]. Primary care physicians and specialists manage rhinosinusitis with equivalent technical efficiency, with primary care physicians providing less costly treatment [5]. Chronic rhinosinusitis has a high economic burden; in 2007, total expenditures in the United States were estimated to be $8.6 billion [4].

Risk Factors

Rhinosinusitis is more common in patients with comorbid asthma and allergic rhinitis [6]. Other predisposing factors are listed in Table 1 [2]. Studies investigating the relationship between smoking and rhinosinusitis are conflicting [4].

Microbiology

The vast majority of cases of acute rhinosinusitis are viral in etiology. The incidence is high; the average adult is affected an estimated 2–5 times per year. Secondary bacterial infection is uncommon and complicates only 0.5–2 % of cases [7]. The two most common bacterial causes of rhinosinusitis are *Streptococcus pneumoniae* and *Haemophilus influenzae*. Less common pathogens include *Moraxella catarrhalis*, *Streptococcus pyogenes*, and *Staphylococcus aureus* [1].

Clinical Presentation

The classic clinical presentation of rhinosinusitis includes nasal congestion, mucopurulent nasal discharge, facial pain or pressure, and fever. Associated symptoms include anosmia, hyposmia, aural fullness, cough, headache, and toothache [2, 8].

Diagnosis

The diagnosis of bacterial rhinosinusitis is clinical. Previous studies have used criteria based on symptoms (Table 2) [1, 9]. The diagnosis of rhinosinusitis requires the presence of at least two major criteria or one

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Table 1 Predisposing factors for rhinosinusitis

Systemic	Viral URI
	Allergy/asthma
	Immotile cilia (e.g., Kartagener syndrome)
	Cystic fibrosis
	Immune disorder
	Gastrointestinal reflux disease
Local	Trauma
	Rhinitis
Mechanical	Choanal atresia
	Deviated septum
	Polyps/foreign body
	Hypertrophy of turbinate or adenoids

Source: Ref. [2]

Table 2 Conventional criteria for the diagnosis of sinusitis

Major symptoms	Minor symptoms
Purulent anterior nasal discharge	Headache
Purulent or discolored posterior nasal discharge	Ear pain, pressure, fullness
	Halitosis
Nasal congestion or obstruction	Dental pain
Facial congestion or fullness	Cough
Hyposmia or anosmia	Fever (for subacute or chronic sinusitis)
Fever (for acute sinusitis only)	Fatigue

Source: Ref. [1]

major plus two minor criteria. Diagnoses made by these criteria correlated with radiographic evidence of sinus involvement, but did not distinguish between a bacterial and viral etiology. For this reason, the Infectious Diseases Society of America (IDSA) has adopted guidelines based on characteristic patterns that take into account duration, severity, temporal progression, and "double sickening" to differentiate bacterial from viral rhinosinusitis [1]. The diagnosis of bacterial rhinosinusitis requires any of the three following clinical presentations: (a) *persistent* symptoms or signs compatible with acute rhinosinusitis lasting for at least 10 days without improvement, (b) *severe* symptoms or either fever of at least 39 °C or purulent nasal discharge or facial pain lasting for at least 3–4 consecutive days at the onset of illness, and (c) *worsening* symptoms or signs including new onset of fever, headache, or increased nasal discharge that were initially improving 5–6 days following an upper respiratory infection.

Physical Exam

The IDSA guidelines mentioned previously are the cornerstone of diagnosis, but the following physical exam findings support a suspected diagnosis of bacterial rhinosinusitis: purulent nasal discharge, nasal obstruction, sinus tenderness, nasal mucosal erythema and edema, and/or infraorbital venous pooling [8, 10, 11]. No validated studies have examined the predictive value of specific signs more likely to be associated with a bacterial rather than viral etiology [1].

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Diagnostic Imaging and Laboratory Studies

Although rhinosinusitis is a clinical diagnosis, there are particular settings in which imaging may be useful. Plain radiography is universally recognized as neither useful nor cost effective [12]. Computed tomography is the preferred imaging modality. Imaging may be considered in the following situations: severe or recurrent disease, suspected complications, immunocompromised states, and prior to surgery [7–9]. It should be noted, however, that the severity of symptoms does not correlate with CT findings [13]. Nasal endoscopy, while it allows for better visualization of nasal purulence compared to anterior nasal exam, is often impractical for primary care physicians and is not essential for diagnosis [12]. Cultures obtained from endoscopic aspirates or sinus puncture are considered the gold standard for confirming a bacterial versus viral etiology [14] in order to identify causative organisms in patients with complicated rhinosinusitis, who are immunosuppressed, or who are refractory to treatment [7, 9]. However, these tests are invasive and lack feasibility in primary care settings [14].

Treatment

Antimicrobial Therapy

Antibiotic therapy should be initiated once the clinical diagnosis of bacterial rhinosinusitis has been established by the IDSA criteria previously described. Antibiotics initiated in this setting shorten the duration of illness, offer more prompt symptomatic relief, and prevent recurrence and suppurative complications [1]. Standard-dose amoxicillin-clavulanate (875 mg/125 mg twice daily), rather than amoxicillin alone, is recommended as first-line treatment due to the high prevalence of β-lactamase-producing *H. influenzae* [1]. However, standard-dose amoxicillin-clavulanate is inadequate for penicillin-non-susceptible (PNS) *S. pneumoniae*, which have a mutation in the penicillin-binding protein 3 that is unaffected by the addition of a β-lactamase inhibitor. Thus, in patients with certain risk factors, high-dose amoxicillin-clavulanate (i.e., 2 g/125 mg twice daily) is recommended as first-line treatment. Risk factors for PNS include residence in geographic regions with high (≥10 %) endemic rates of PNS *S. pneumoniae*, severe infection (e.g., signs of systemic toxicity with fever of ≥39 °C [102 °F]), age >65 years, recent hospitalization, patients who are immunocompromised, or antibiotic use within the past month [1]. Respiratory fluoroquinolones are also highly active against PNS *S. pneumoniae* and *H. influenzae*, but are not superior to β-lactam antibiotics [1]. Options for patients with β-lactam antibiotic allergy include doxycycline (100 mg twice daily or 200 mg daily), levofloxacin (500 mg daily), or moxifloxacin (400 mg daily).

Adjunctive Therapies

Symptomatic management may include analgesics, antipyretics, intranasal glucocorticoids, hydration, and possibly nasal saline irrigation [1, 15].

Intranasal glucocorticoids are helpful in reducing or relieving symptoms compared to placebo when used as monotherapy or as an adjunct to antibiotics. Higher doses have a stronger effect on relieving symptoms without a significant increase in adverse effects [16].

The benefit of nasal saline irrigation is unclear, but is relatively safe and may reduce time off from work. Minor adverse effects, such as dry nose and irritation, are experienced by fewer than half of users. The optimal concentration, frequency, volume, and technique for irrigation have not been determined [17].

There is little evidence that topical or oral decongestants provide benefit as adjunctive treatment to antibiotics based on symptom scores, histologic changes, or radiographic findings [1]. However, some patients do report symptomatic improvement, so decongestants may be considered for patients with viral rhinosinusitis for whom antibiotic therapy is not indicated [1]. Topical decongestants should be used with

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caution, however, since they can trigger rebound congestion and inflammation, especially when used for more than 3 days.

There is also scant evidence that antihistamines provide significant relief in patients with rhinosinusitis, but they may be beneficial in patients with concomitant allergic rhinitis [1]. First-generation antihistamines should be avoided in the elderly, who are more susceptible to anticholinergic effects [18].

Both decongestants and antihistamines should be avoided in children under 2 years of age. The use of these medications may increase morbidity, and a small number of deaths in this population have been reported [19].

Mucolytics thin mucus and improve nasal drainage, but there is no evidence supporting their effectiveness in rhinosinusitis [8].

Systemic steroids or leukotriene inhibitors may be considered in chronic rhinosinusitis, especially in patients with nasal polyps [2, 20, 21].

Chronic Rhinosinusitis

There is a lack of consensus about treatment for chronic rhinosinusitis, likely due to its inherent heterogeneity [12, 15]; therefore referral to an otolaryngologist is warranted in cases of acute rhinosinusitis that do not improve after maximal medical therapy or recurrent infections (defined as 3–4 episodes per year) [1, 7]. In such cases, predisposing medical conditions, such as immunodeficiency, allergic disease, diabetes mellitus, or immotile cilia syndrome, should be considered.

Surgical Management

Surgery is reserved for patients with chronic rhinosinusitis who have failed maximal medical therapy (typically defined as therapy for 4–6 weeks) or who have underlying anatomic abnormalities as well as clear demonstration of rhinosinusitis by CT imaging or endoscopic examination [2, 15]. 90 % of adult patients experience symptomatic improvement after surgery. Surgical intervention is rarely indicated in children [2].

Tonsillopharyngitis

The subjective complaint of sore throat is often described clinically as pharyngitis, but multiple contiguous anatomic structures – including the tonsils, adenoids, nasopharynx, posterior pharynx, uvula, and soft palate – are stretched with swallowing and perceived as odynophagia when inflamed [22]. Thus, in this chapter, discomfort, pain, and scratchiness of the throat will be referred to as one entity: *tonsillopharyngitis*.

Epidemiology

Tonsillopharyngitis is among the most common reasons for primary care visits [23], accounting for 6 % of visits by children to family physicians and pediatricians [24]. Throat-related symptoms were the 14th most common reasons for physician visits in 2010 [25] and the 9th most common reason for emergency room visits in 2011 [26]. The estimated economic burden of group A streptococcal tonsillopharyngitis specifically has been estimated to be between $224 and $539 million annually, with children missing an average of 4.5 days of school and parents missing 1.8 days of work in order to care for them [27].

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Etiologies

Infectious

The most common cause of tonsillopharyngitis is viral infection. Common viruses include rhinovirus, coronavirus, adenovirus, parainfluenza, influenza, echovirus, reovirus, respiratory syncytial virus, herpes simplex virus, coxsackievirus, and Epstein-Barr virus [28, 29]. Bacterial causes include streptococci, *Corynebacterium diphtheriae*, *Neisseria gonorrhoeae*, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae*. Group A streptococcus (GAS) is the most common bacterial cause. Thrush, most commonly caused by *Candida* species, can also cause sore throat [28].

Inflammatory

Inflammatory causes of tonsillopharyngitis include laryngopharyngeal reflux, allergic rhinitis with postnasal drip, foreign body, chronic mouth breathing, mucositis, muscle tension dysphonia, vocal cord granuloma, rheumatoid arthritis, gout, pemphigus, and Kawasaki's disease [28].

Clinical Presentation of GAS Tonsillopharyngitis

The characteristic presentation of GAS tonsillopharyngitis includes abrupt onset of sore throat, odynophagia, fever, headache, abdominal pain, nausea, and vomiting [23]. Physical exam findings may include tonsillopharyngeal erythema and exudate, a beefy-red and swollen uvula, soft palate petechiae, anterior cervical lymphadenopathy, and a scarlatiniform rash.

Laboratory Diagnosis

The Infectious Disease Society of America (IDSA) guidelines recommend testing for GAS tonsillopharyngitis by rapid antigen detection test (RADT) and/or culture to distinguish GAS from viral tonsillopharyngitis, except when features such as oral ulcers, rhinorrhea, cough, and/or hoarseness strongly suggest a viral etiology [30]. In children and adolescents, a throat culture should be sent after a negative RADT to rule out infection, since the sensitivity of throat culture is 90–95 % while that of the RADT is 70–90 %. A backup culture is not necessary after a positive RADT, as the test is highly specific (approximately 95 %) [30].

Complications of GAS Tonsillopharyngitis

Suppurative Complications

Peritonsillar abscesses are most commonly seen in patients between ages 20–40 with recurrent or chronic tonsillopharyngitis that has been inadequately treated [29]. The abscess develops in the space between the lateral aspect of the tonsil and the pharyngeal constrictor muscle [29]. Peritonsillar abscess can be difficult to distinguish from severe tonsillopharyngitis, as both can present with asymmetric tonsillar hypertrophy and drooling. The hallmark of peritonsillar abscess, however, is trismus, which results from inflammation and pus that has tracked above the pterygoid region [28]. Other characteristic symptoms include a muffled "hot potato" voice, severe unilateral sore throat, edema of the ipsilateral soft palate, and deviation of the uvula [28]. When the diagnosis is in question, ultrasonography (transcutaneous or intraoral) or CT imaging can aid in identifying an abscess and thus distinguish from peritonsillar cellulitis [31]. If there is concern for spread of infection into the lateral neck, contrast imaging with MRI or CT is indicated.

Retropharyngeal abscesses affect younger children, typically between 1 and 5 years of age. The characteristic presentation includes neck stiffness, dysphagia, odynophagia, and high fever following

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an upper respiratory infection [28]. The airway can be affected and, depending on the degree of obstruction, can manifest as a muffled voice, drooling, trismus, stridor, tachypnea, or tripod positioning. There may be external neck swelling. Immediate consultation with an otolaryngologist and anesthesiologist is warranted given the potential for life-threatening airway compromise. Once the patient is stable, imaging should be obtained. CT of the neck with contrast is the modality of choice [28].

Other suppurative complications of GAS tonsillopharyngitis include cervical lymphadenitis, sinusitis, otitis media, and mastoiditis [32].

Nonsuppurative Complications

Nonsuppurative complications of GAS tonsillopharyngitis are postinfectious and immunologically mediated and include acute rheumatic fever, acute poststreptococcal glomerulonephritis, and poststreptococcal reactive arthritis [32].

Treatment of GAS Tonsillopharyngitis

All patients with uncomplicated GAS tonsillopharyngitis should be treated with antibiotic therapy. Treatment accomplishes three objectives: (1) prevention of both suppurative complications and acute rheumatic fever; (2) decreased communicability, which allows patients to return to work or school; and (3) shortened duration of illness [23]. First-line treatment options are penicillin (250 mg twice to three times daily in children, 250 mg four times daily or 500 mg twice daily in adolescents and adults) or amoxicillin (50 mg/kg daily with a maximum dose of 1,000 mg/day) for 10 days. Penicillin-allergic patients may be treated with a first-generation cephalosporin such as cephalexin (20 mg/kg/dose twice daily with a maximum of 500 mg/dose) or cefadroxil (30 mg/kg daily with a maximum of 1,000 mg/day) for 10 days, clindamycin (7 mg/kg/dose twice daily with a maximum of 300 mg/dose) for 10 days, or azithromycin (12 mg/kg once daily with a maximum of 500 mg/day) for 5 days [30]. There is no evidence that one antibiotic is superior to another [33].

Adjunctive treatment with acetaminophen or nonsteroidal anti-inflammatory agents can be useful in controlling fever and pain [23]. Complementary therapies, including acupuncture, herbal and dietary supplements, have not been shown to be beneficial [34].

Treatment of peritonsillar abscess includes hydration, incision and drainage under local anesthesia, and antibiotics aimed at both aerobic and anaerobic bacteria [28, 29]. Tonsillectomy is indicated if incision and drainage fails to completely drain the abscess [29].

Treatment of retropharyngeal abscess involves immediate intravenous antibiotic therapy aimed at gram-positive aerobes and anaerobes [28]. Small (<2 cm) retropharyngeal abscesses can often be treated with antibiotics alone, but if a patient fails to improve after 48 hours of therapy, incision and drainage is indicated [28].

Chronic Carriers, Recurrent Infection, and Asymptomatic Contacts

Chronic carriers have GAS present in the pharynx but no immunologic response to the organism [30]. In temperate climates during the winter and spring months, as many as 20 % of school-aged children are asymptomatic carriers. Antimicrobial therapy is generally not indicated in these patients, as they are not likely to be contagious or develop suppurative or nonsuppurative complications [30]. However, there are certain indications where eradication of GAS carriage should be considered: during a community outbreak of acute rheumatic fever, in the context of poststreptococcal glomerulonephritis or invasive GAS infection, during an outbreak of GAS tonsillopharyngitis in a closed or partially closed community, the presence of a personal or family history of acute rheumatic fever, in a family with significant anxiety about GAS infections, or when tonsillectomy is under consideration solely because of carriage [30].

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There are several explanations for patients with recurrent episodes of GAS tonsillopharyngitis: repeated viral infections in a chronic GAS carrier, noncompliance with antibiotic therapy, or a new infection acquired from a close contact [30]. Test of cure is not indicated, as antibiotic failure is rare if taken as prescribed. If "ping-ponging" of infection within a family is suspected, simultaneously obtaining RADT or cultures from all members and treating those that are positive is reasonable [30].

Asymptomatic contacts should not be treated. Antibiotic prophylaxis of household contacts with penicillin has not been shown to decrease the incidence of developing subsequent GAS tonsillopharyngitis [30].

Tonsillectomy

Tonsillectomy is one of the most common procedures performed in the United States, with more than 530,000 carried out on children younger than 15 years of age each year [35]. The American Academy of Otolaryngology recommends tonsillectomy for children with 7 episodes or more of tonsillopharyngitis in the past year, 5 episodes or more per year in the past 2 years, or 3 episodes or more per year in the past 3 years. Tonsillectomy has been shown to improve quality of life in children with recurrent tonsillopharyngitis by reducing the number of throat infections, healthcare provider visits, and need for antibiotic therapy [35]. Children who have more severe or frequent episodes of tonsillopharyngitis may benefit more from tonsillectomy than less severely affected children [35]. Tonsillectomy may also be beneficial in patients with multiple antibiotic allergies, PFAPA syndrome (periodic fever, aphthous stomatitis, pharyngitis, and adenitis), and recurrent peritonsillar abscess [35]. There is limited evidence on the effectiveness of tonsillectomy in adults with recurrent tonsillopharyngitis [36], but there is some retrospective data that there is a positive and prolonged effect on quality of life, especially with regards to younger patients with more severe symptoms [37].

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Family Medicine
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Sexually Transmitted Diseases

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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 improved 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 1.4 million cases in 2012. Females have higher rates of infection 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 [6]. In addition, all pregnant women 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

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

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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 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].

The following antibiotics and regimens are recommended [7]:

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 base	500 mg	By mouth four times daily	7 days
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

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 and undergo repeat testing 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

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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 334,826 cases of gonorrhea reported in the United States in 2012, making it the second most common reported STI [4]. There are a slightly higher number of cases in women than men. This infection occurs most commonly in persons between the ages of 15 and 24 years.

Screening

The CDC recommends that all sexually active women with risk factors, such as multiple or new sexual partners, be screened annually [4]. In addition, all pregnant women 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 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. Patients who are likely to fail to comply with a 7-day course of treatment should receive single-dose treatment. All patients

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who test positive for gonorrhea should also be evaluated for other sexually transmitted infections 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 250 mg intramuscularly in one dose with the addition of either azithromycin 1 g orally in a single dose or doxycycline 100 mg by mouth twice daily for 7 days. 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 in a single dose.

Penicillin/Cephalosporin Allergy

If the patient has an allergy to cephalosporins, azithromycin 2 g orally in one dose is administered. Because of concerns for resistance, any patient treated with an alternative therapy should have a test-of-cure culture 2 weeks after treatment and any positive cultures should undergo antimicrobial susceptibility testing [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, she may take azithromycin 2 g orally in one dose as an alternative.

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 [9]. Similar to chlamydia, EPT should only be utilized in very selective cases in populations at high risk for HIV and should never be used in partners who are exhibiting signs of more severe infection [9].

Trichomoniasis

Trichomoniasis, caused by the protozoan *Trichomonas vaginalis*, is the most common nonviral sexually transmitted infection in the world [13]. An estimated 3.1 % of the US population is infected but only 30 % develop symptoms of infection [4]. 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 [7].

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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 60–70 % sensitive. 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* is also detected through culture of vaginal secretions, liquid-based pap cytology, and NAAT or PCR of vaginal, endocervical, or urine specimens [7].

The diagnosis of *T. vaginalis* in men is more challenging, as wet preparation is not sensitive. 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

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 is less than 50 % effective in treating trichomoniasis. 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 and it is not due to reinfection, it should be considered to be resistant. 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 5 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 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; EPT can be considered if necessary [9].

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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 is the most common gynecologic reason for inpatient hospital admission in the United States [16]. Multiple organisms have been implicated in PID including *N. gonorrhea*, *C. trachomatis*, *G. vaginalis*, and anaerobes such as *B. fragilis*, most likely beginning with an ascending infection originating in the cervix and creating the opportunity for entry of other organisms [6, 13]. 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, 13].

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 F (38.3 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

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 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 the table below [7].

Parenteral Treatment

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 8 h for a total of 14 days
Clindamycin 900 mg IV every 8 h *and*	Doxycycline 100 mg orally twice daily for a total of 14 days	Choose clindamycin over doxycycline for subsequent oral therapy

(*continued*)

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Recommended regimen	Subsequent oral therapy	Tubo-ovarian abscess present
Gentamicin at 2 mg/kg of body weight in an IV or IM loading dose, followed by 1.5 mg/kg every 8 h	*or* 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 8 h for a total of 14 days

See Ref. [7]

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 below [7].

Outpatient Treatment Options

Recommended regimen	Additional anaerobic coverage
Ceftriaxone 250 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 250 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]

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 listed below, although this is not ideal given the emergence of quinolone-resistant *Neisseria gonorrhoeae*. Patients empirically treated with quinolones or another alternative regimen for gonorrhea should have a culture performed for test of cure 14 days after treatment. This will allow susceptibility testing of the organism in case of treatment failure [7].

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Treatment in Patients with Severe Penicillin/Cephalosporin Allergy

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	+/− Metronidazole 500 mg PO twice daily for 14 days	Add azithromycin 2 g orally as a single dose

See Ref. [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 [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 2012, a total of 15, 667 cases of primary and secondary syphilis were reported to the CDC, with 75 % of cases reported in MSM populations [4].

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 to 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, 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

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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 dark-field 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 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

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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].

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Pregnancy

In order to prevent congenital syphilis in the fetus, all pregnant patients must be treated with 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 [16]. 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 and provider-applied, 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

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therapy. Side effects of treatment include hypo- or hyperpigmentation, scarring, chronic pain, and rarely systemic effects [7].

Patient-Applied

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	Uncertain
Imiquimod 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

See Ref. [7]

Provider-Applied

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
Podophyllin resin 10–25 %	Air-dry fully before contact with clothing. Wash area 1–4 h after application	Every week as needed	Application should be limited to $<$0.5 mL of podophyllin or an area of $<$10 cm^2 of warts per session. The area to which treatment is administered should not contain any open lesions or wounds		Unknown
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

See Ref. [7]

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Alternative regimens include 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 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. Male circumcision is also thought to reduce transmission of HPV [7].

Genital Herpes

Herpes simplex virus (HSV) 1 or 2 causes genital herpes, although genital infection is most often 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. Tzanck preparation can be used; however, it is discouraged, as it is

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not sensitive or specific. A patient's serum can also be tested for type-specific serum antibodies. HSV-1 serum antibodies may be caused by a previous oral infection that often occurs in childhood. Patients with HSV-2 are more likely to have recurrences and have increased occurrences of asymptomatic viral shedding [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 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]. Additionally, research shows that single-day, high-dose patient-initiated episodic therapy may offer yet another option for episodic treatment. Both famciclovir 1500 mg in a single dose and famciclovir 750 mg twice daily for one day have been shown to significantly reduce time of healing. The convenience of one-day treatment may improve patient adherence and may be particularly effective in patients who experience fewer recurrent episodes [21].

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 [7]. Herpes infection requires multiple measures to decrease this risk, as newborn infection can be fatal. Patients are given antiviral therapy starting at 36 weeks of gestation and are delivered via cesarean if active lesions or prodromal symptoms are present during labor [20].

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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].

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 Prevention Training Centers found at http://www.stdhivpreventiontraining.org [7].

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Human Immunodeficiency Virus Infection and Acquired Immunodeficiency Syndrome

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Contents

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In the arc of a generation, physicians, chemists and pharmacists, nurses, public health specialists, community activists, patients, and their loved ones have transmuted an illness of immense suffering and certain death into a largely manageable illness, dependent on resources and health information.

Family physicians have a large role to play: patient care, transmission-reduction education, community health education, patient advocacy, and public health measures all require our expertise.

Up-to-date information is essential; protocol changes and new medications require frequent updates to provide the best care:

www.ucsf.edu/hivcntr (warm-line: Ron Goldschmidt)

www.cdc.gov

www.hivatis.org

www.iasusa.org

Natural History

The illness was first described on June 5, 1981, with the landmark *Morbidity and Mortality Weekly Report* 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 1959 from human remains and lab specimens in central Africa. Two genetic strains of HIV have been identified, type 1 and type 2. HIV type 1 is the cause of 98 % 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 USA 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 dramatically reduces transmission, and recently preexposure 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 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 [1].

Screening and Diagnosis

An estimated 250,000 persons in the USA have HIV infection and are not aware they are infected [2]. In the USA, females, blacks, Hispanic/Latinos, and older individuals are more likely to

experience delays in diagnosis [3]. 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 [4]. Worldwide, more than 30 million people are infected [5]. More than 75 % of all people infected with HIV are in sub-Saharan Africa, and AIDS is the leading 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 [6].

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 [8]. 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 [9].

In the USA, direct to consumer in-home HIV testing is available utilizing saliva and is becoming more widely available in other countries [10]. 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 [11].

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 to 2 weeks after transmission of the virus. If that testing is indeterminate, HIV nucleic acid (viral load) testing is employed. Western blot confirmation is no longer recommended [12].

Symptoms by HIV Stage

Acute HIV Infection

Acute infection represents a burst of viral replication and is marked by fatigue, fever, myalgias, and arthralgias, 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 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, multidermatomal 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

Preexposure Prophylaxis (PrEP)

Both the CDC and the World Health Organization (WHO) recommend the daily use of preexposure 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 [13]. Currently, only one antiretroviral combination (tenofovir/emtricitabine marketed as Truvada) is approved for this indication by the US FDA.

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 [14].

Acute or Suspected Exposure (Postexposure 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 needlestick) 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 USA can be assessed by calling the National Clinician's Post Exposure Prophylaxis Hotline 24 h a day at 888-448-4911. While postexposure 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 postexposure 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 [15].

Postexposure 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 [16].

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
Coreceptor tropism assay	If consideration is being given to the use of a CCR5 antagonist

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 [17]. 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) [18] (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.

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 vulnerable, latent or active TB treatment, and treatment for hepatitis B and/or C for those found to be coinfected. 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 considered in some circumstances.

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, control of HIV is the goal for now. 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 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)

Four different 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. 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 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 [19].

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 [20]. 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 [21].

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 [22].

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 [23].

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 [24].

GI Tract and Liver

Lactic acidosis can result from antiretroviral treatment for HIV, presenting as fatigue, myalgia, nausea, and abdominal pain [25]. Pancreatitis is seen frequently in patients with HIV, both due to the infection and as a side effect of treatment [26]. 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 [27].

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 [28]. Avascular necrosis of bone is not uncommonly seen [29].

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 [30].

HIV in Children

The number of HIV-infected children in the USA 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 [31]. 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- 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 [32].

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 % [31]. HIV disproportionately affects African American babies in the USA (www.cdc.gov/hiv/risk/gender/pregnantwomen/facts). 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 candidal 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 [33].

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 [34] (www.womenshealth.gov/hiv-aids/).

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 [35] (www.AIDSinfo.net).

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. In addition,

care for patients with HIV looks hopeful, with better medications, better disease management, less stigma, and longer healthier lives.

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Bacteremia and Sepsis

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General Principles

Public Health and Economic Burden

Sepsis is the sixth most common reason for hospitalization in the United States [1], with severe sepsis being the leading cause of in-hospital death [2]. Over 750,000 people develop sepsis annually, and almost one in four of these people die [1, 2]. Sepsis has an in-hospital mortality rate of approximately 16 %; this is eight times higher than other stays [1].

From 1997 to 2008, the cost of treating patients hospitalized for sepsis in the United States increased by almost 12 % annually. This increase may be attributed to an aging population with more chronic illnesses, greater use of invasive procedures, immunosuppressive drugs, chemotherapy, transplantation, and increasing microbial resistance to antibiotics. Hospitalization rates for sepsis increase with advanced age; patients over 65 years account for more than two thirds of sepsis hospitalizations in the United States [1, 3]. Globally, it is estimated that 18 million people are diagnosed with sepsis annually [4]. The case-fatality rate depends on the setting and severity of disease. Mortality can be as high as 30 % for sepsis, 50 % for severe sepsis, and 80 % for septic shock [5]. *Escherichia coli* is the most commonly identified organism in patients with a primary diagnosis of sepsis, while methicillin-resistant *Staphylococcus aureus* (MRSA) is most common for patients with a secondary diagnosis of sepsis [3].

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 [6]. Bacteremia often occurs transiently without any clinical consequences.

Systemic inflammatory response syndrome (SIRS) is an uncontrolled inflammatory response to an insult without probable or documented infection [7]. The clinical manifestations of SIRS are often identical to those occurring in sepsis and may occur in a number of conditions (Table 1). Therefore, it is important to exclude sepsis when SIRS is diagnosed. Excluding sepsis is often a challenge, as microbiological investigations are often negative for various reasons including antibiotic administration prior to sample collection or technical issues related to blood culture. Only 30–60 % of patients diagnosed with sepsis have positive blood cultures [9]. Negative or inconclusive blood cultures do not exclude the possibility of sepsis in patients when there is a high index of suspicion. In the clinical setting, the diagnosis of sepsis is often made retrospectively.

Sepsis is defined as a known or suspected infection plus systemic manifestations of infection [10].

Severe sepsis is sepsis with infection-induced organ dysfunction or infection-induced acute tissue hypoperfusion. Organ dysfunctions associated with sepsis include acute lung injury, acute kidney injury, coagulopathy, liver dysfunction, and cardiovascular abnormalities. Sepsis-induced tissue hypoperfusion abnormalities include hypotension, elevated lactate, oliguria, and altered mental status [10].

Septic shock is defined as sepsis-induced hypotension which is not responsive to adequate fluid resuscitation [9].

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Table 1 Causes of the systemic inflammatory response syndrome (SIRS) [8]

Differential diagnosis of sepsis
Anaphylaxis
Sterile inflammation, e.g., vasculitis, acute pancreatitis
Hypovolemia
Acute blood loss
Chemical aspiration
Acute respiratory failure
Acute myocardial infarction
Diabetic ketoacidosis
Adrenal insufficiency
Transfusion reaction
Acute mesenteric ischemia
Autoimmune disorder
Substance abuse or intoxication
Drug overdose
Inborn errors of metabolism

Multiple organ dysfunction syndrome (MODS) is a progressive organ dysfunction in an acutely ill patient such that homeostasis cannot be maintained without intervention. It is at the severe end of the severity spectrum of both SIRS and sepsis.

The sepsis spectrum begins with infection, which progresses to bacteremia, sepsis, severe sepsis, septic shock, and death.

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, 10, 11].

The most common sites of infection are the respiratory, genitourinary, and gastrointestinal systems, as well as the skin and soft tissue [12]. These sites account for over 80 % of all cases of sepsis [13]. Among nursing home residents 65 and older, the urinary tract was found to be the most common source of sepsis [14].

Overall, fever is often the first manifestation of sepsis [12]. However, neonates, immunocompromised or chronically ill patients, and the elderly may have sepsis without meeting the sepsis criteria. Therefore, clinical suspicion is key to appropriate and timely diagnosis. In the elderly, for example, failure to eat, withdrawal, agitation, disorientation, and confusion may be early signs of sepsis [12, 15]. 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 necessitating a more detailed history.

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 should not delay early initiation of life-saving care. General and hemodynamic

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Table 2 Sepsis spectrum diagnostic criteria [16]

Sepsis	Documented or suspected infection and some of the following:
	General variables:
	Fever > 38.3 °C
	Hypothermia (core temperature < 36 °C)
	Heart rate > 90/min or > 2 standard deviations (SD) above the normal value for age
	Tachypnea
	Altered mental status
	Significant edema or positive fluid balance > 20 mL/kg over 24 h
	Hyperglycemia (plasma glucose > 140 mg/dL or 7.7 mmol/L) in the absence of diabetes
	Inflammatory variables:
	Leukocytosis (WBC count > 12,000/μL)
	Leukopenia (WBC count < 4,000/μL)
	Normal WBC count with > 10 % immature forms
	Plasma C-reactive protein >2 SD above the normal value
	Plasma procalcitonin > 2 SD above the normal value
	Hemodynamic variables
	Arterial hypotension (SBP < 90 mmHg, MAP < 70 mmHg, or a SBP decrease > 40 mmHg in adults, or < 2 SD below normal for age)
	Organ dysfunction variables
	Arterial hypoxemia (PaO_2/FiO_2 < 300)
	Acute oliguria (urine output < 0.5 mL/kg/h for at least 2 h despite adequate fluid resuscitation)
	Creatinine increase > 0.5 mg/dL or 44.2 μmol/L
	Coagulation abnormalities (INR > 1.5 or aPTT > 60 s)
	Ileus (absent bowel sounds)
	Thrombocytopenia (platelet count < 100,000/μL)
	Hyperbilirubinemia (plasma total bilirubin > 4 mg/dL or 70 μmol/L)
	Tissue perfusion variables
	Hyperlactatemia (>1 mmol/L)
	Decreased capillary refill or mottling

variables that may indicate sepsis (Table 2) should be carefully noted to aid in the early identification of patients in the sepsis spectrum.

Diagnosis

Laboratory Workup and Imaging

Laboratory findings consistent with sepsis are as outlined in Table 2. Routine laboratory workup for sepsis includes two sets of blood cultures (drawn before starting antibiotics if possible). Urinalysis, urine culture, and cultures from other suspected sites (wound, respiratory secretions, CSF, or other body fluids) are also appropriate. Other laboratory tests and imaging studies should be individualized based on history and physical examination findings.

Lactate levels have been strongly correlated with mortality [17, 18].

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Table 3 Surviving Sepsis Campaign care bundles [10, 16]

To be completed within 3 h of presentation:
1. Measure lactate level
2. Obtain blood cultures prior to administration of antibiotics
3. Administer broad spectrum antibiotics
4. Administer 30 mL/kg crystalloid for hypotension or lactate ≥4 mmol/L
To be completed within 6 h of presentation:
5. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥65 mmHg
6. In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L (36 mg/dL):
(a) Maintain adequate central venous pressure (CVP) [a]
(b) Maintain adequate central venous oxygen saturation ($ScvO_2$)[a]
7. Remeasure lactate if initial lactate was elevated[a]

[a]Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mmHg, $ScvO_2$ of ≥70 %, and normalization of lactate

Differential Diagnosis

Various conditions can mimic sepsis. Although the differential is very broad, Table 1 includes common causes of SIRS other than sepsis.

Treatment

Aggressive and timely management of patients with sepsis is paramount. Expeditious transfer to an inpatient setting should occur. 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 considered.

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 [16].

The Surviving Sepsis Campaign (SSC) care bundle (Table 3) 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 [19, 20].

Prevention

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 [21]. Early identification and appropriate treatment of infection

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in all patients especially those at increased risk of sepsis reduces chances of progression to bacteremia and sepsis. Good nutrition and lifestyle changes (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 under-recognized 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 [22]. 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. 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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The focus of this chapter is on toxoplasmosis, Rocky Mountain spotted fever (RMSF), trichinosis, giardiasis, psittacosis, Ebola virus, Lyme disease, and hantavirus. Most of these illnesses are zoonotic in nature. Physicians should be familiar with their diagnosis, evaluation, and treatment.

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.*

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 non-sporulated oocysts, which become infective within 1–5 days after defecation. Freezing, chemical, or physical treatment (such as chlorine or ozone treated) does not destroy sporulated oocysts; only heating >55 °C reliably destroys them [1].

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 method of acquisition is via blood transfusion or solid organ transplantation from an infected donor [2].

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 organism lies dormant in eye, muscle, or brain tissue and is not eliminated [3].

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. Other 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. 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 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 [4].

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.

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/

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.

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 [5].

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 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 [5]. 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 [6].

Rocky Mountain Spotted Fever

Family physicians should be cognizant that Rocky Mountain spotted fever (RMSF) is the most common rickettsial infection in the USA. Early diagnosis is critical since it has a high mortality rate if untreated [7].

Epidemiology

Rocky Mountain spotted fever (RMSF) is a zoonotic tick-borne disease in which humans are accidental hosts. RMSF is caused by *Rickettsia rickettsii*, an obligatory intracellular gram-negative bacterium. RMSF is transmitted by the American dog tick (*Dermacentor variabilis*), by the Rocky Mountain wood tick (*Dermacentor andersoni*), and by the brown dog tick (*Rhipicephalus sanguineus*); it is also transmitted by the *Amblyomma cajennense* ticks in Central and South America. Adult *Dermacentor* ticks act as both vector and reservoir for human infection. Ticks become infected by feeding on the blood of infected animals, through molting, or by transovarial passage. The organisms in turn invade the endothelial and smooth muscle cells of blood vessels which cause generalized vascular injury and activation of inflammatory and coagulation mechanisms. The majority of the reported cases of RMSF occur between April and September [8].

Clinical Features

The incubation period of RMSF is 2 days to 2 weeks. The initial diagnosis of RMSF is based on clinical manifestations. Early manifestations of the disease are spiking fever (95–100 %), severe headache (80–90 %), and myalgia, fatigue, gastrointestinal discomfort, and rash involving palms and soles (56–88 %) [9, 10]. Rash is present in 90–100 % of children with RMSF and usually appears on first or second day of illness [11]. Blanching red macular or papular rash usually starts on the wrists and ankles, spreading to palms and soles and then centripetally to arms, legs, and trunk. Within 2–3 days, it may become petechial and purpuric. In a few patients, the rash may progress to skin necrosis or gangrene of the digits or limbs, requiring amputation in severe cases. In some cases, individuals do not develop a rash at all [9, 12]. Neurologic involvement may include meningismus, encephalitis, focal neurologic deficits, hearing loss, seizures, and coma

[13]. Cardiac involvement is rare and may be manifested as myocarditis, pericarditis, or arrhythmias [14]. Pulmonary symptoms may include cough, dyspnea, frank pulmonary edema, adult respiratory distress syndrome, and pulmonary infiltrates on chest x-rays. Acute renal failure from hypovolemic hypotension may develop in severe RMSF.

RMSF may be confused with measles in unimmunized patients; the rash starts on the face and progresses to the rest of the body. Cough, coryza, and conjunctivitis are typical of the disease and very unusual in RMSF. Meningococcal rash may be petechial at one point, but usually becomes necrotic quite early. Meningococcemia usually presents with fulminant petechiae on hands and feet but can involve the entire body; meningeal signs are often marked.

Laboratory Diagnosis

The diagnosis of RMSF is mainly clinical because serological confirmation usually is delayed and inadequate (77 %) [15]. Most patients with RMSF have a normal white blood cell count at presentation. As the illness progresses, thrombocytopenia becomes more prevalent and may be severe; thrombocytopenia may result from increased destruction at sites of rickettsia-mediated vascular injury. Other findings that are common in advanced cases include hyponatremia, elevations in serum aminotransferases and bilirubin, azotemia, and prolongation of the partial thromboplastin and prothrombin times. Hyponatremia is a particularly common finding in patients with central nervous system involvement. The cerebrospinal fluid (CSF) analysis may demonstrate pleocytosis; elevated CSF protein is seen in approximately in one-third of patients.

Seroconversion usually occurs at least 2 weeks after the onset of symptoms. Indirect fluorescent antibody (IFA) is the most widely available and most frequently used test. IFA is 94–100 % sensitive after 14 days of illness [16]. The diagnostic titer is usually a dilution greater than 1:64 or a fourfold rise in titers between acute and convalescent sera collected more than 2 weeks apart and run in parallel. Detection of *R. rickettsii* antigen on skin biopsy specimen with direct immunofluorescence or rickettsial DNA in blood or tissue by PCR is used when available.

Treatment

Tetracycline (or related derivatives such as doxycycline) and chloramphenicol are the only two antibiotics with proven clinical efficacy in treating RMSF. Doxycycline is most successful when given in the first 5 days of illness. It is the drug of choice for treating adults (100 mg every 12 h for 7 days) and children (2.2 mg/kg/dose every 12 h, max 100 mg/dose). Chloramphenicol 50–75 mg/kg/day in four divided doses for 7 days is used when tetracycline is contraindicated; children should receive 12.5–25 mg/kg dose every 6 h. The drugs should generally be continued for 2 days after the patient has become afebrile. Tetracycline or chloramphenicol should be given intravenously in patients with marked nausea and vomiting or if otherwise severely ill. Fluid and electrolyte maintenance is important in managing this illness. Without treatment, death may occur within 8–15 days in 20 % of patients. Patients with the highest risk for fatal disease include children younger than 10 years of age or older than 70 years old, African-American males, alcoholics, and patients with G6PD deficiency [17].

Prevention

Some of the preventive measures include the use of protective clothing, tick repellants N, N-diethyl-3-methylbenzamide (DEET) on the skin, permethrin used on the clothes, and daily complete body tick check while in endemic areas. Removal of ticks requires care using forceps, grasping the tick as close to the skin as possible without compressing the body head, and then pulling straight outward with gentle traction.

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) [18].

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. *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 [19].

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

Most infections are subclinical. However, infection with a heavy load of larvae may lead to clinical features of the enteric phase including diarrhea (most common), abdominal discomfort, and vomiting. The systemic 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 [20]. Conjunctivitis, subungual hemorrhages, and maculopapular rash may be observed. 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 mainstays of treatment are anthelmintics, 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.

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*.

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.

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 [21]. 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. There they replicate and can cause symptoms of diarrhea and malabsorption. The transmission cycle is complete when the trophozoites are exposed to biliary acid, transform into cysts in the jejunum, and then are passed in the feces [22].

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 produces partial immunity to disease and leads to a reduced risk of reinfection and to reduced development of overt symptoms in secondary infection [23].

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 (sulfur smell), 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 [24].

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, microscopy may be cumbersome and requires an experienced laboratory technologist. The Food and Drug Administration (FDA) has approved an antigen detection test for *Giardia*, *Cryptosporidium*, and *Entamoeba histolytica*. The only test cleared by the FDA so far is the multiplexed Luminex xTAG GPP [25].

Treatment

Several agents are used to treat giardia infection and include:

- Nitroimidazoles: Tinidazole (adults 1–1.5 g daily for 1–2 days, children 40 mg/kg/day for 1–2 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 and penetrates body tissues/fluids such as saliva, breast milk, semen, and vaginal

secretions. 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 7–10-day course. It is approved for use against *Giardia*. Side effects might include nausea, vomiting, and diarrhea.
- Benzimidazoles: 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 [26].

Ebola Viral Disease and Marburg Disease

Etiology and Epidemiology

Ebola (EBOV) and Marburg viruses (MARV) are the members of family *Filoviridae* causing Ebola virus disease and Marburg disease in humans and nonhuman primates. These are enveloped, non-segmented, negative-stranded RNA viruses. According to World Health Organization (WHO), until now, there have been only 25 epidemics of Ebola virus reported, but the 2014 outbreak was the largest epidemic ever reported. MARV currently consists of a single species: Lake Victoria MARV. The EBOV consists of five species; they are named according to the location of the first outbreak recorded by this strain: Zaire Ebola virus, Sudan Ebola virus, Ivory Coast or Tai Forest Ebola virus, Bundibugyo Ebola virus, and Reston Ebola virus. Zaire Ebola virus and Sudan Ebola virus have high fatality rates [27]. Reston virus is not pathogenic in humans. There is some evidence suggesting that bats can act as hosts and as a reservoir for filoviruses. MARV is often introduced into human populations by people who enter caves and mines, and EBOV may be introduced by hunting for or processing "bush meat" (the meat of wild animals that may include nonhuman primates).

Filoviruses are highly infectious and enter the body through mucous membranes or breaks in the skin or by direct parenteral transmission. Virus can be spread to others through direct contact with body fluids or fomites or from infected bats or primates. Body fluids including blood, feces, vomit, saliva, breast milk, urine, sweat, nasal secretions, semen, and genital secretions are infective. First, Ebola virus attacks the macrophages and dendritic cells and then is carried to regional lymph nodes via lymphatics and subsequently to the liver, spleen, and adrenal gland via the blood stream. EBOV may attack many organs causing necrosis (liver, spleen, adrenal, kidney, gonads, gastrointestinal tract, and endocardium).

In most infectious diseases, precautions and actions need to be initiated before a diagnosis is made to protect against the spread to others. Thoughtful screening of patients as well as staff returning from endemic areas is essential, especially to a person who has both consistent signs or symptoms and risk factors as follows: elevated body temperature or subjective fever or symptoms, including severe headache, fatigue, muscle pain, vomiting, diarrhea, abdominal pain, or unexplained hemorrhage, *and* an epidemiologic risk factor within the 21 days before the onset of symptoms. A comprehensive action plan to promptly and effectively identify, isolate, and treat a potential case has been developed from the Centers for Disease Control and Prevention (CDC). The link below provides valuable information pertaining to endemic areas, virus transmissibility, symptoms, current management, and isolation recommendations http://www.cdc.gov/vhf/ebola/index.html. Complete information is provided, including case definition, symptoms, transmission of the virus, infection control precautions, and diagnostic process. A specific

process has been outlined to maintain consistency, communicate with key staff, and promptly identify and isolate a potential case.

Early recognition is critical to controlling the spread of Ebola virus. Healthcare providers should evaluate the patient's epidemiologic risk, including a history of travel to a country with widespread Ebola virus transmission or cases in urban settings with uncertain control measures or contact within the preceding 21 days with a person with Ebola while the person was symptomatic.

If a diagnosis of Ebola is being considered, the patient should be isolated in a single room (with a private bathroom), and healthcare personnel should follow standard, contact, and droplet precautions, including the use of appropriate personal protective equipment (PPE). Infection control personnel should be contacted immediately.

If Ebola is suspected, the 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 [28].

Clinical Presentation

The incubation period ranges from 2 to 21 days. Patients usually present with nonspecific symptoms such as fever (87 %), fatigue (76 %), anorexia (65 %), vomiting (67 %), diarrhea (66 %), abdominal pain (45 %), and unexplained bleeding (18 %) and also may present with cough, rhinorrhea, headache, or myalgia [29]. In the 2014 outbreak, the primary clinical presentation was gastrointestinal (severe diarrhea). Hemorrhagic manifestations include maculopapular rash and mucosal bleeding, usually in the gastrointestinal and genitourinary tracts. Altered mental status, septic shock, and bleeding are poor prognostic factors. Major causes of death are electrolyte imbalance, shock, and multi-organ failure. Fatalities typically occur in the second week after infection. Ebola virus disease should be considered in patients with the relevant clinical symptoms and exposures in an endemic area. 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

The main diagnostic test is detection of viral genome by reverse transcription polymerase chain reaction (RT-PCR). The virus is usually detectable 48 h after infection. Antigen capture ELISA may be used. Immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies are detected by ELISA later in the disease course or after recovery.

Treatment

Currently, the only treatment available is supportive care. Early treatment including fluid replacement, electrolyte balance, and management of concomitant infections improves survival. Rehydration with oral or intravenous fluids (Ringer's lactate solution is preferred) is based on the patient's hemodynamic status. Several gene-based vaccines including rAd5, CAdVax, VSV, and HPIV 3 (recombinant adenovirus, vesicular stomatitis virus, human parainfluenza virus) have been developed and need further human trials [30]. Some drugs like favipiravir, TKM-Ebola, BCX-4430, AVI-6002, and ZMapp have shown some efficacy and are still undergoing clinical experimental trials.

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.

Lyme Disease

Lyme disease (LD) was initially diagnosed in the town of Lyme, Connecticut, after an unusual cluster of what appeared to be juvenile rheumatoid arthritis. Subsequently, a spirochete *Borrelia burgdorferi* (Bb) was isolated as the agent producing this new clinical entity. Lyme disease is the most common tick-borne illness in the USA. It is transmitted by the deer tick *Ixodes scapularis* in the East, mid-Atlantic, and Upper Midwest and by the *Ixodes pacificus* in the West Coast of the USA, and the *Ixodes ricinus* is the major European vector. The causative organism is a spirochete *Borrelia burgdorferi* (Bb) sensu lato, a fastidious microaerophilic bacterium. This organism has been classified into several genotypes including *B. burgdorferi* sensu stricto, *B. garinii*, and *B. afzelii* (Europe) [31].

Epidemiology

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 *Ixodes* 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 take 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.

Several factors are associated with the risk of transmission of Bb from ticks to humans: the tick must be infected; the duration of tick attachment is a critical factor; after attachment, the tick feeds and becomes engorged, discharging its saliva into the bite wound; and the bacteria live in the midgut of the tick, which needs to be engorged with blood before the bacteria migrate to the salivary gland and the saliva, through which the organism is injected into the host [32]. 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.

The "primary lesion" or "early localized disease" occurs around the tick bite site. The infection is manifested as erythema migrans (EM), which 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. EM appears at the site of tick bite 3–30 days after inoculation. This lesion is found in 90 % of patients with evidence of infection with *Bb*. Another very rare skin lesion is *Borrelia* lymphocytoma, a bluish-red nodule appearing usually on the earlobe or nipples within months or years of an infection (reported from Europe) [33].

The "secondary lesions" of *Borrelia* infection or "early disseminated disease" usually presents with multiple EM lesions; these lesions are smaller but morphologically similar to the initial

lesion (EM). After the initial stage, the spirochete disseminates systemically via lymphatic system or bloodstream. In untreated disease, it affects extracutaneous sites such as joints, CNS, and cardiovascular system. Common manifestations of early disseminated disease include oligoarticular joint disease with arthralgia and myalgia (arthritis is usually a manifestation of late disease), typically with effusion affecting large joints usually the knee; it is asymmetric, accompanied by joint edema without erythema, and waxes and wanes causing joint dysfunction [34]. 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 of Bell's palsy in endemic areas. Cardiac involvement is a less common complication of systemic disease; the presentation may include chest pain, dyspnea, fatigue, palpitations, or syncope and may include some forms of atrioventricular block.

The late stages of borreliosis or "late disseminated disease" usually presents either as chronic arthritis (monoarticular or oligoarticular) or neurological symptoms such as encephalopathy or peripheral neuropathy. Acrodermatitis chronica atrophicans, a chronic sclerosing dermatitis, develops in patients infected with *B. afzelii* an uncommon manifestation in Europe but virtually unknown in the USA. 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.

Differential Diagnosis: Several dermatological conditions can be confused with EM; they may include cellulitis (usually has edema, erythema, warmth, tenderness), erythema multiforme (most lesions are <2 cm in diameter with central clearing and also may have mucosal involvement), contact dermatitis (variable shape, location, and size of lesions usually located around neck, wrist, umbilical areas), spider bites (lesion is erythematous with variable size and associated with a necrotic ulcer), tinea (annular or ringlike lesion), and urticaria (raised erythematous lesion with serpiginous borders).

Diagnosis

Serology, polymerase chain reaction (PCR), and culture can be performed in order to diagnose *Borrelia* infection. 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. The Centers for Disease Control and Prevention (CDC) recommends serologic evaluation as the preferred initial diagnostic test. 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 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. PCR test has the highest sensitivity for Lyme disease in synovial fluid in patients with untreated Lyme arthritis. Urine antigen testing is not recommended [35]. 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 post infection, 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. Repeat serology as a mode of documentation of treatment effectiveness is also not recommended. Lyme serology should not be performed in individuals with vague symptoms: chronic nonspecific maladies, i.e., fatigue, arthralgia, and neurocognitive deficits. Even if there is a positive serology for LD, an individual might have been exposed in the past, and the present symptoms may be related to another pathogen such as babesia, anaplasma, other borrelias, or viruses.

Treatment

Early 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 axetil (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 axetil (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 14–21 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.

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). 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.

Hantaviruses

Hantavirus is named after the Korean River, Hantaan, where the first outbreak was reported in 1951. The ensuing illness from infection has been referred to as Korean hemorrhagic fever. Hantavirus is one of the major classes of zoonotic pathogens and is a member of the *Bunyaviridae* family, which are negative-stranded, spherical, and enveloped RNA viruses [36]. The resulting diseases can cause significant morbidity and mortality and occur globally. Up to 200,000 cases involving hospitalization are reported annually, with most in China. In the USA, there have been outbreaks in the Southwest in 1993 (Sin Nombre hantavirus) and in Yosemite National Park, California, in 2012 [37]. In this outbreak, ten people were infected, three of whom died. Up to 14 viruses in this genus exist, with the most virulent ones causing hemorrhagic fever with renal syndrome (HFRS), with approximately a 15 % mortality, and hantavirus cardiopulmonary syndrome (HCPS), with greater than 40 % mortality.

Rodents are the primary hosts of hantavirus, and occasionally humans acquire the virus, likely via exposure to aerosols of various secretions or excretions. Bites can also transmit the virus.

Human-to-human transmission of hantavirus is exceedingly rare but possible. In the 1993 US outbreak, rodents that were trapped near the patients' homes had the same novel hantavirus genetic identification as those in infected patients' serum. Recent findings indicate that bats, moles, shrews, and other mammals may also serve as hosts [38, 39].

Clinical Presentation

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 [40]. These two syndromes may overlap. Age, gender, genetic response, and immune status can affect the prognosis [41]. 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

Usual findings are thrombocytopenia, increased hematocrit, leukocytosis, and elevated creatinine. IgG and IgM antibodies can be detected at the onset of clinical symptoms using ELISA, immunoblot, or immunofluorescence techniques. PCR techniques offer faster results.

Treatment

Treatment is generally supportive, with earlier intervention leading to better outcomes. The patient may need intubation and supplemental oxygen, as well as intravenous fluid therapy. Early dialysis helps in acute renal failure. Intensive treatment for hypotensive shock and pulmonary edema is also necessary to improve outcomes. Early administration of ribavirin may reduce renal damage. In China, inactivated virus preparations for active immunization have been used, but currently no licensed vaccines exist against hantavirus in the USA.

Prevention

In general, rodent control is via sealing gaps/holes in homes, setting traps, and keeping food in enclosed containers. An excellent resource for prevention can be found at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5109a1.htm.

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Complementary and Alternative Medicine

Mathew Devine and Meg Hayes

Contents

Integrative medicine (IM) can be defined as healing-oriented medicine that takes account of the whole person (body, mind, and spirit). It emphasizes the therapeutic relationship and makes use of all appropriate therapies, both conventional and alternative [1]. The field of integrative medicine is a diverse collection of more than 1000 practices and principles that are used as a form of healing. In the 1990s, the term "integrative medicine" (IM) replaced the terminology complementary and alternative medicine (CAM). IM is now used to describe these techniques that were not previously identified as acceptable treatments in western medical practice.

In general, IM practices and techniques are not taught in allopathic medical schools. Since the US population is increasingly using integrative medicine principles and practices, some academic health centers have started to offer education in medical school and beyond. In 1997 an integrative medicine fellowship was started at the University of Arizona. Since that time other integrative medicine fellowships have been implemented and are available to primary care physicians. The Consortium of Academic Health Centers for Integrative Medicine (CAHCIM) currently represents over 60 academic health centers and affiliate institutions in the USA, Canada, and Mexico. Integrative medicine training is also available in a fourth year model for many family medicine residencies across the country. NIH-sponsored R-25 grants have also been awarded to many academic centers

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Table 1 Top 10 most common integrative medicine therapies

Order of most commonly used therapies	Integrative medicine technique	Licensure status	Systemic review (s) of evidence
1	Natural products/herbal medications	Supplements are exempt from FDA approval	Yes
2	Deep breathing	Can be advised by any type of provider or self-taught	Yes
3	Meditation	Can be advised by any type of provider or self-taught	Yes
4	Osteopathic manipulation and chiropractic treatment	Licensure needed for D.O. and D.C. in the USA	Yes
5	Massage	Licensure required in most US states	Yes
6	Yoga	Certification available no formal licensure needed in the USA	Yes
7	Diet-based therapies	None unless seeing certified dietician or licensed naturopath	Depends on diet studied
8	Progressive relaxation	No formal licensure/certification required	Yes
9	Guided imagery	No formal licensure/certification required	Yes
10	Homeopathic therapy	Certification/diploma but no licensure required	Yes

to include some of these principles in their medical school curricula [1].

A study conducted in 2002 by the Centers for Disease Control and Prevention's (CDC) National Center for Health Statistics (NCHS) indicated that 62 % percent of adults used some form of IM therapy specifically for health reasons during a prior 12-month period, when the definition of IM therapy included prayer. When prayer specifically for health reasons was excluded from the definition, 36 % of adults used some form of IM therapy during the prior 12 months [2]. The same agency conducted another survey/study in 2007, and Table 1 lists the ten most commonly used IM treatment in US adults from 2002 to 2007 [3].

This chapter outlines current use of integrative medicine practices and provides a brief description of some of the more commonly used methods of IM. A full discussion of each of the methods is beyond the scope of this chapter. Table 2 lists other types of IM practices that are also performed but not as often as those listed on Table 1. Some of the items listed in Table 2 will be discussed in this chapter. Additional informational resources for all of the treatments discussed can be reviewed in Table 3. Guidelines for the selection of integrative medicine providers as resources for referral will also be reviewed. Since this area continues to grow and these techniques are sought and used by patients, family physicians are well advised to become knowledgeable in this area.

Natural Products/Herbal Medicine

Herbs, botanicals, and plants have been used medicinally by humans as far back as the earliest civilizations. The pharmaceutical industry has a long history of using plant-derived products to create their products. It has been estimated that 50 % the approved pharmaceutical drugs during the last 30 years are derived either directly or indirectly from natural products [4]. In 2007, the sales of herbal products accounted for more than 25 billion dollars in sales yearly, and they are used for many conditions [4]. The popularity of herbal medications relates to increasing availability and acceptability of IM by the general population, concerns regarding use of allopathic medications, increasing desire for preventative medicine, and

Table 2 Other types of IM treatments that are used that clinicians should be knowledgeable of

Integrative medicine techniques/ treatments	Licensure status	Systemic review(s) of evidence
Acupuncture	Licensure required	Yes
Aromatherapy	Not required	Limited
Ayurveda	Not required	Yes
Biofeedback	Not required	Yes
Energy psychology	Not required	Yes
Environmental medicine	Not required	Yes
Feldenkrais	Not required	Limited
Hypnotherapy	Required in select US states	Yes
Naturopathy	Required in most US states	Yes
Reflexology	Only in 2 states	Yes
Reiki	May need massage license in certain areas	Limited
Shiatsu	May need massage license in certain areas	Limited

self-advocacy by patients seeking alternatives to allopathic medications that have failed to treat conditions or have caused side effects. Herbal products may be viewed as "natural" and therefore healthier and safer than allopathic medications. Patients may not notify their physicians of their use of herbal medications for fear of nonapproval of this practice. Herb–drug interactions are well documented, and it is important for patients to be explicitly asked about all substances and treatments taken, whether prescribed or over the counter.

The most definitive source of information on herbal medicine is the German Commission E. This commission has examined the evidence for use of more than 380 herbs. Evidence considered included clinical studies, chemical data, experimental pharmacologic studies, traditional use, case reports, and other data available to assess the safety and efficacy of herbal medications. While criticism has been leveled that many of these sources lack scientific rigor, the Commission E monographs remain the most authoritative source of information on these widely used compounds. The monographs are available in paper and electronic formats [5].

Standardization of herbal medication is complicated by the natural properties of plants, which contain numerous chemical compounds. The conditions under which the plant is grown, harvested, and processed can affect the chemical composition, and the various components of the plant, leaves, roots, and flowers may have different effects or uses. In addition, often it is not known which of the components is responsible for the desired effect. Standardized extracts are available and should be used preferentially, but many herbal preparations are not labeled to include the precise composition [6]. In the USA, the Food and Drug Administration (FDA) does not regulate herbal substances. The 1994 Dietary Supplement Health and Education Act (DSHEA) placed herbal products into a new class identified as "dietary supplements" and limited the authority of the FDA to regulate herbs as they do medications [7]. Dietary supplements, including herbals and botanicals, vitamins, minerals, and amino acids, are exempt from FDA approval or monitoring, provided that they do not claim to treat or prevent disease. Dietary supplements must carry the following disclaimer: "This product has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease." Supplement labels can claim to maintain health or function, such as "maintains normal cardiovascular function," but cannot claim to "reduce blood pressure" without FDA approval. Table 4 lists documents ten of the most commonly used herbal medication, as well as contraindications and side effects [8].

Table 3 Sources of information on integrative medicine treatments and practitioners

Integrative medicine techniques/ treatments	Agency and contact information
Integrative medicine	National Institute of Health, National Center for Complementary and Alternative Medicine: www.ncaam.nih.gov
Natural products/herbal medications	MedlinePlus: dietary supplements: http://www.nlm.nih.gov/medlineplus/ http://www.nlm.nih.gov/medlineplus/druginformation.html Office of dietary supplements http://ods.od.nih.gov/
Deep breathing	Dr.Weil.com – Official Website of Andrew Weil M.D. http://www.drweil.com/drw/u/ART00521/three-breathing-exercises.html
Meditation	For more information on transcendental meditation: http://www.tm.org/
Osteopathic medicine	American Osteopathic Association – www.osteopathic.org Osteopathic Cranial Academy – www.cranialacademy.org
Chiropractic care	American Chiropractic Association – www.acatoday.org
Massage	American Massage Therapy Association – www.amtamassage.org
Yoga	International Association of Yoga Therapists: www.iayt.org
Diet-based therapies	Celiac disease: www.celiac.org Elimination diet: http://www.webmd.com/allergies/guide/allergies-elimination-diet
Progressive relaxation	www.guidetopsychology.com/pmr.htm
Guided imagery	www.fammed.wisc.edu/our-department/media/mindfulness
Homeopathic therapy	National Center for Homeopathy – www.homeopathycenter.org
Acupuncture	American Academy of Medical Acupuncture (MD and DO acupuncturists)- www.medicalacupuncture.org National Acupuncture and Oriental Medicine Alliance – www.nccaom.org
Aromatherapy	National association for holistic aromatherapy: https://www.naha.org/
Ayurveda	National Ayurvedic Medical Association http://www.ayurvedanama.org/
Biofeedback	Association for Applied Psychophysiology and Biofeedback: http://www.aapb.org/
Energy psychology	Association for Comprehensive Energy Psychology: http://www.energypsych.org/
Environmental medicine	American Academy of Environmental Medicine: http://www.aaemonline.org/
Feldenkrais	The Feldenkrais method: www.feldenkrais.com/
Hypnotherapy	American Society of Clinical Hypnosis: http://www.asch.net/
Naturopathy	American Association of Naturopathic Physicians: www.naturopathic.org
Reflexology	Reflexology Association of America: http://reflexology-usa.org/
Reiki	The International Center for Reiki training: http://www.reiki.org/
Shiatsu	American Organization for Bodywork Therapies of Asia http://www.aobta.org/

Table 4 Uses of common herbal medications [8]

Herb	Uses/effects	Contraindications	Side effects	Systemic review (s) of evidence
Echinacea	Promotes natural resistance to infection – used many in upper respiratory infections	Systemic illness such as HIV, TB, and MS	Chills, fever, nausea, allergic reaction	Yes
Garlic	Hyperlipidemia	None	Avoid before surgery – potentiates warfarin	Yes
Ginkgo biloba	Dementia, cognitive impairment	With a known hypersensitivity to ginkgo; caution in depression	Stomach upset, headache, skin reaction	Yes
Saw palmetto	Symptoms of benign prostatic hypertrophy	None known	Gastric upset	Yes
Ginseng	Fatigue, weakness, physical performance	Hypertension, excessive caffeine use	Possible interaction with MAOI	Yes
Grape seed extract	Venous insufficiency, possibly with certain types of cancers	Not to be used with a known allergy to grapes	Headache, itchy scalp, dizziness, and/or nausea	No
Green tea	Cancer treatment, cognitive impairment, GI illnesses	Can interact with many medications	In excess can cause same SE as caffeine does	No
St. John's Wort	Mild to moderate depressive mood, anxiety	None known, but not recommended with other antidepressants, specifically MAOIs	Trouble sleeping, vivid dreams, fatigue	Yes
Bilberry	Vision impairment	Caution with diabetic and anticoagulant medications	Rash	No
Aloe	Dermatitis, wound healing	As PO supplement can act as laxative	Burning/skin irritation	Yes

Mind–Body Medicine

Prayer is the most widely used form of IM [2]. It is widely used by those afflicted with serious illnesses and diseases. Due to the large variation of prayers and it uses amongst different religions and cultures the full scope of this important treatment is beyond the scope of this chapter.

Four other common IM techniques (listed in Table 1) are from the field of mind–body medicine: deep breathing, meditation, progressive relaxation, and guided imagery. These four techniques support improved relaxation. It has been demonstrated that many of these techniques can impact the functioning of the autonomic nervous systems (ANS). Divided into the sympathetic and parasympathetic nervous systems, the ANS has long been thought to relate to bodily functions that operated below the level of one's conscious awareness or control. The following techniques are easily learned and can be incorporated into daily life for cost-effective health benefit:

1. **Deep breathing** and breathing exercises are useful in focusing a patient's 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. This focus can replace any troubling thought or images that may have preceded an episode of hyperventilation, while slowing the breath, prolonging the expiratory phase, and resolving an associated alkalosis.

2. **Meditation** is a term used for a broad practice that involves using techniques that help to promote relaxation, expand one's emotional capabilities, and improve mindfulness and internal health. This practice has roots from many different cultures and religions across the world. Due to the ongoing different styles of practice of meditation, there is no formal consensus on what is defined as the accepted criteria on the process and the outcomes that one needs to perform in order to achieve or be in a state of meditation.
3. **Progressive muscle relaxation** and body scans are used to reduce muscle tone. In progressive relaxation, the patient first holds tension in a muscle group for several seconds and then consciously relaxes it before moving on to repeat this exercise throughout the body. In body scan, the patient starts at the head or feet and consciously relaxes a portion of the body one segment at a time. These techniques can be aided by the use of a scripted audiotape to guide the patient through the complete exercise.
4. **Guided imagery** cues the imagination to stimulate physiologic changes. Just as one may experience sympathetic excitement with images such as a frightening scene in a movie, the opposite can be achieved with appropriate images. For example, learning to warm the hands by imagery suggesting the holding of a warm mug of cocoa or the ambient heat of a campfire can result in a significant temperature change in the fingertips due to increased blood flow.

Mind–body interventions pose little risk or contraindication. The interventions can offer significant symptom relief from chronic pain and distressing symptoms due to illness while providing patients with a powerful sense of control, thus engaging them in active participation in their health care. These techniques are frequently useful alone and may also be employed as adjunctive treatment to standard care. Mind–body interventions can be taught in brief office visits and have the potential to improve the quality and decrease the cost of health care [9].

Manual Medicine

Osteopathic and chiropractic manipulation as well as massage therapy are widely used for musculoskeletal complaints such as headache, neck, and low back pain. Manipulation has also been found to be of value in repetitive strain injury, chronic fatigue syndrome, lumbar back pain, fibromyalgia, rheumatoid, and osteoarthritis. The benefit of manipulation is likely due to both the local effects on muscles and ligaments as well as psychological relaxation, both of which can reduce pain and increase function [10]. Studies also demonstrate patient preference for manual treatment of acute low back pain, whether through osteopathic, chiropractic, or massage [2].

Osteopathic Manipulation

The field of osteopathy was started in 1874 by Andrew Taylor Still, MD, DO. The term "osteopathy" was created by Still since at the time his hypothesis was that the pathology of most conditions stems from the bones themselves. Though this theory was not proven to be true, other aspects of the field of osteopathic medicine are still currently part of the US landscape as an integrative medicine technique primarily for treatment of musculoskeletal conditions. Osteopathic practitioners are present throughout the world. The degrees of training and licensing process vary from country to country. In the USA, an individual must attend a 4-year medical school to receive a degree as a doctor of osteopathic medicine.

Once a D.O. degree is obtained in the USA, these physicians can practice the full scope of medicine. Integrated into the curriculum for US osteopathic medical students are the principles and practices of osteopathic manipulative technique (OMT). OMT is a body-based treatment that offers a conservative, noninvasive option for relieving pain while also attempting to improve function and mobility to the area being treated. OMT is an integrative medicine technique that has an evidence base for improvement of function

Table 5 Contraindications to performing osteopathic manipulation

Condition	Reason associated with condition to not perform OMT
Spinal osteomyelitis	If history of IV drug use and/or skin infection within the preceding 3 months caution prior to treatment should be performed
Spinal fracture	Caution advised if had spinal trauma within the preceding year and/or corticosteroid use exceeding 3 months duration within the last year
Herniated disk	Caution advised with a history of leg pain radiating below the knee, history of persistent numbness or weakness in the leg or legs, or history of claudication
Ankylosing spondylitis	If condition has not been identified, consider work up if patient has morning back stiffness and individual is younger than 40 years of age
Cauda equina syndrome	With a current history of bladder dysfunction, saddle anesthesia, or fecal incontinence treatment should not be rendered
Cancer	Treatment should be delayed until further work up is performed for patients with previous history of cancer, excluding nonmalignant skin cancer, and/or unexplained weight loss of at least 10 lbs or 5 % of body weight within the preceding year, and/or no relief of low back symptoms with conservative treatment for persons older than 50 years after 6 weeks duration
Pregnancy	Treatment can be used however would use caution with high velocity techniques

related to treating the following conditions: back pain [11], asthma [12], acute ankle sprain [13], and otitis media [14]. There are many other conditions that can be treated with OMT; however, most treatments tend to involve the spine. In addition, D.O.s are taught techniques that can be used over the entire body. Other common areas for OMT involve the following regions: pelvis, shoulders, knees, ribs, and the paranasal sinuses.

The use of OMT greatly depends on the field of medicine that a D.O. pursues. In the USA, there are specialty D.O.s that practice full-time manipulation therapy. Osteopathic physicians trained in primary care often use OMT as an adjunct to practice. If referral is considered, it is important to ask if the referring D.O. physician actively practices OMT and also to ensure that their skills are up to date.

The use of OMT is generally safe. Complications are reported to occur in approximately one in a million treatments [15]. Despite the safety record, it is important to carefully select patients to exclude those with contraindications to therapy. See Table 5 for contraindications to OMT.

There are multiple types of treatments that can be used for OMT. Treatment is tailored based on the location and type of pain/somatic dysfunctions that is being treated. Treatments can be performed using direct or indirect methods. If the practitioner engages the restrictive barrier, this is a direct treatment. If the practitioner moves tissue and/or joints away from the barrier, this is referred to as indirect treatment. OMT can also be performed with the patient assisting in the treatment (active), or when the patient is relaxed (passive), allowing the clinician to move the body tissues. Table 6 shows a list of the types of OMT treatments that are commonly used.

There is ongoing national research in primary-care-oriented OMT. These studies may provide further evidence for the use of OMT in the primary care setting. It is important to note that OMT is not only reserved for D.O. practitioners. Additionally, training in OMT can be integrated into allopathic residency training and is within the unrestricted scope of practice for MDs. Courses and curricula are available to teach MDs these techniques and principles.

Chiropractic Care

Chiropractic treatments focus on the relationship between the structure of the spine and healthy body function. Chiropractic treatment may include spinal manipulation, applications of heat or cold, dietary and activity recommendations, and the prescription of nutritional supplements.

Table 6 Commonly used osteopathic manipulation techniques

Treatment type	Brief description of treatment	Direct or indirect treatment	Active or passive
Myofascial release/ soft tissue technique	Directed to the soft tissue structures of the body	Both	Both
Muscle energy technique	Aimed the involved joint and muscles restriction of motion. Patient uses the opposite muscular to attempt to increase the barrier of restriction in the area being treated	Direct	Active
Counterstrain	Gentle technique that identified "tender points" in muscles, ligaments, or tendons, and then these areas are shortened with specific positioning and held for greater than 90 s at a time	Indirect	Passive
High velocity low amplitude	This technique uses a controlled force that is a quick movement over a small distance aimed at joints of the spine. There is a low velocity high amplitude technique that can apply a slow force over a greater distance as well	Direct	Passive
Cranial	Technique using the cranial bone motion and balancing the tension membranes of the nervous system	Both	Passive
Ligamentous articular strain	Similar to cranial technique except instead uses the ligaments attached to the joints of the body	Indirect	Passive
Facilitated positional release	Positional-based technique with the clinician providing a facilitated force in the form of compression/torsion to the soft tissue or spine for a brief interval	Indirect	Passive
Active release technique	Technique that patient is guided by clinician uses voluntary muscle contraction and possible respiratory effort as well	Both	Active
Visceral manipulation	Techniques to the viscera area to treat GI tract and pelvic organ dysfunctions	Direct	Passive
Fluid motion technique	Designed to move fluid in different parts of the body, examples include sinus drainage and lymph movement through thoracic channels	Indirect	Passive

Chiropractors have accredited education standards, and licensure is required to practice in every state. The profession enjoys a high level of recognition, with an estimated 1 in 15 Americans seeing a chiropractor annually. There are more than 50,000 chiropractors in practice in the USA, and the World Federation of Chiropractic has representation from 70 countries. Medicare, workers' compensation programs, and many private insurers cover chiropractic services.

Chiropractic treatment has integrated into the health-care system as the result of a professional emphasis on research that has defined the benefits and risks of spinal manipulation using accepted outcome measures. Studies have demonstrated beneficial effects of spinal manipulation on the duration and severity of acute low back pain and short-term positive results in chronic low back pain [16], although studies have not demonstrated substantial long-term effects on pain [17].

Referral to a chiropractor may be considered for treatment of acute, uncomplicated back and neck pain or for a short course of treatment for chronic pain and nonprogressive sciatica. Other conditions that may be improved include headaches that originate from the cervical spine and symptoms of otitis media [18].

Chiropractic treatment of nonmusculoskeletal conditions is controversial, and to date there are not adequate data on effectiveness. Anecdotal reports of improvement of menstrual cramps, asthma, and functional gastrointestinal symptoms exist, but it will be some time before data concerning any definitive effect in these disorders are available. Contraindications to chiropractic manipulation include conditions where bony structures are susceptible to trauma such as acute 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.

Massage Therapy

Massage therapy is the manipulation of soft tissue and connective tissue with the intention of maintaining or improving health by affecting changes in relaxation, circulation, lymphatic flow, and increased range of motion. Most states have licensing requirements that must be met before a practitioner can use the title "massage therapist." Empirical support exists for the efficacy of massage therapy in reducing pain, increasing alertness, diminishing depression and anxiety, enhancing immune function, and improving sleep patterns. Specifically, massage therapy has been found to be valuable in reducing anxiety levels in patients undergoing surgery under local anesthesia [19], facilitating mother–infant interaction for mothers with postpartum depression [10], and decreasing pain and anxiety and improving sleep in patients with low back pain [20].

Massage therapy can be considered for a number of conditions. Contraindications to massage include contagious or irritative skin disorders, edema due to heart or kidney failure, fever, infections spread by blood or lymph circulation, and leukemia or lymphoma.

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 has gained popularity in the USA and is used as method to try and improve health by focusing on controlling one's breathing, working on maintaining postures, and using meditation to help promote relaxation and balance.

Based on the survey in 2007 by the CDC, of those who reported participating in IM activities, yoga was used by 6.1 % [3]. There have been a large number of clinical trials testing the benefits of yoga. From all of the studies that have been published, yoga has performed most favorable in those that suffer from various chronic diseases. Each style has different certification, training, and ongoing continuing education requirements. To practice yoga in the USA, national or state licensure is not needed. Even though licensure is not needed, many practitioners pursue yoga certification that is available from multiple national or international organizations. These organizations operate independently are not part of any formal body to oversee all of the different types of yoga training and certifications.

Diet-Based Therapies

There has been increased understanding in diet-based therapies and food safety since the start of the twenty-first century. Depending on one's geographic region, it is important to be aware of the possible harmful exposures from one's environment. The possible environmental exposures could be from exposure to pesticides, growth hormones and antibiotics, as well as from genetically modified foods. These factors and others have led patients to seek out practitioners to see if they have sensitive or an allergy that needs treatment. These food allergies and reactions can promote or cause certain conditions to arise. Food allergy prevalence also appears to be increasing among children and adults [21].

There is a growing trend to use elimination diets to help restore health for an individual who has a food allergy or food reaction. An elimination diet is the process of removing certain foods from the diet to decrease inflammation and decrease ongoing immune-mediated reactions. Elimination diet should be discussed and planned with the patient. The process is usually to plan the elimination diet and to provide the patient with foods that they should avoid. Then depending on the intensity of the program, those foods are to be avoided for a set period – usually between 2 and 4 weeks [22]. If the symptoms improve during that time, then it is plausible that the food could

have been the agent that was causing the problem. However, with chronic problems, the condition may take longer than that time frame to improve. In this case, a challenge phase can be used to add the agent back into their diet to test whether the symptoms worsen or return if the food is reintroduced. After that time, a long-term diet plan can be created with the patient based on these results.

There is increasing evidence regarding foods that should be added to one's diet for certain health benefits. One example of this is the anti-inflammatory diet. It has been estimated that significant numbers of chronic conditions could be prevented by adhering to a healthy diet [23]. There are many types of anti-inflammatory diets. These generally focus on reducing the amounts of red meat, sodium, dairy, and carbohydrates in the diet. Specific dietary therapies that can be used for treatment are beyond the scope of this chapter.

Homeopathy

First developed in the eighteenth century, homeopathy has been rising in popularity since the latter part of the twentieth century. The basic tenets of homeopathy include curing illness with highly diluted substances that at full strength cause the symptoms being treated. The theory is that this process creates a "healing crisis" in which symptoms may worsen before improving. Occasionally the homeopathic medicines are too strong and require a substance or remedy to counteract the effect called an antidote. Many allopathic medications and treatments may function as antidotes and may make patients who are taking homeopathic remedies reluctant to take other medications.

Classical homeopathy is highly individualized and relies on the skill of the practitioner to determine the remedy for a particular person. Similar patients might require different approaches. This has complicated attempts to standardize treatments for scientifically controlled trials, and there is little work that compares homeopathy to allopathic medications [24]. Homeopathic medications are available over the counter for specific conditions, and because classical homeopathy is highly individualized, consultation with an experienced practitioner is recommended.

Numerous training courses and programs provide instruction in homeopathy, but no diploma or certification is currently recognized in the USA to practice homeopathy. There are no national standards or licensing requirements, but both allopathic and naturopathic physicians may use homeopathy as a part of their practice.

Traditional Chinese Medicine (TCM)

Qi (pronounced "chee") is thought to be the vital force that circulates throughout the 12 primary and 8 accessory channels known as meridians to protect, nourish, and animate living beings. Although TCM treatments are used to mend disease states, the central purpose, or higher wisdom, is to maintain the body's order and balance by preserving the conditions within which life thrives. Disease states are thought to result from internal and external causes that disturb balance, such as that between yin and yang. Treatment is aimed at correcting the imbalance through disbursement or replenishment of the disrupted element within the body. Traditional Chinese medicine (TCM) includes the practice of acupuncture, moxibustion (the burning of the herb mugwort to tonify acupuncture needles, or used alone to warm acupuncture points), massage, herbal therapy, and qi gong, a meditative physical exercise. All of these modalities are employed to improve the flow of qi. TCM practice is based on thousands of years of practice and recorded case histories, or "wisdom that has stood the test of time."

Acupuncture

For the treatment of pain, acupuncture analgesia has been shown to be more effective than placebo, indicating that there is a physiologic mechanism present [25]. Nearly every state in the USA has laws regulating acupuncture practice. There are 55 acupuncture schools in the USA [26]. Many

licensed physicians and dentists acquired their acupuncture licenses through continuing education, and several universities offer acupuncture courses to both post and predoctoral students of health science. It is postulated that the penetration of the acupuncture needle stimulates small-diameter nerves in muscles, which then send impulses to the spinal cord. These impulses activate three centers – the spinal cord, midbrain, and pituitary – to release endorphins and the monoamines serotonin and norepinephrine, which act to suppress pain transmission to the cortex at multiple synaptic levels [27]. Further, at the level of the pituitary gland, adrenocorticotropic hormone (ACTH) is released in equimolar amounts to endorphin, thus stimulating cortisol production by the adrenal cortex [28]. This may explain why acupuncture has been found to be helpful in the relief of bronchospasm in asthma and inflammation of arthritis.

The World Health Organization recognizes more than 40 conditions for which acupuncture may be useful (Table 7). Areas of active research regarding acupuncture treatment efficacy include addiction, stroke rehabilitation, hypertension, attention-deficit/hyperactivity disorder, and major depressive disorder. Americans most commonly seek acupuncture treatment for the relief of chronic pain, particularly for arthritis and low back pain [29]. Clinical studies have demonstrated efficacy in chemotherapy- and anesthesia-induced nausea and for postsurgical dental pain. In some cases, it has been found that the combination of acupuncture and standard pharmaceutical treatment is superior to either modality used alone.

In 1996 the FDA reclassified acupuncture needles from the investigational class III status to a class II device and required the use of sterile, nontoxic needles that bear a labeling statement restricting their use to qualified practitioners. Complications associated with acupuncture are relatively rare. The reported occurrence of adverse events is only about 50 cases over a 20-year period in the USA [19]. Reported complications have included pneumothorax and other organ injury, transmission of infectious disease, syncope, bleeding, dyspnea, chest pain, dermatitis, and migration of broken needle fragments [30]. Contraindications to acupuncture include bleeding disorders, skin infections, and valvular heart disease (insertion of semipermanent needles only). Electro-acupuncture should not be used for patients with pacemakers, cardiac arrhythmias, or epilepsy. Caution also must be exercised in pregnant women, as stimulation of some acupuncture points may stimulate uterine contractions.

Table 7 The World Health Organization recognizes traditional Chinese medicine (TCM) treatment of over 43 common disorders

Gastrointestinal disorders
Food allergies, peptic ulcer, chronic diarrhea, constipation, indigestion, gastrointestinal weakness, anorexia, gastritis
Urogenital disorders
Stress incontinence, urinary tract infection, sexual dysfunction
Gynecological disorders
Dysfunctional uterine bleeding, infertility in women and men, premenstrual syndrome
Respiratory disorders
Emphysema, sinusitis, allergies, asthma, bronchitis
Musculoskeletal and neurologic disorders
Arthritis, migraine headaches, neuralgia, insomnia, dizziness, low back pain, neck pain, shoulder pain
Cardiovascular disorders
Hypertension, angina pectoris, arteriosclerosis, anemia
Emotional and psychological disorders
Depression and anxiety, attention-deficit/hyperactivity disorder
Addictions
Alcohol, nicotine, and drugs
Eye, ear, nose, and throat disorders
Ear infection, serous otitis, sinusitis, tinnitus

Naturopathy

Naturopathy is not a single discipline, but represents a wide variety of practices and techniques that are combined into a philosophy of healing [31]. Naturopaths may utilize herbal medications, homeopathy, diet and exercise, stress management, hydrotherapy, massage, and many other modalities in an individualized approach for

each patient. Naturopathic physicians (NDs) are trained as primary care physicians in 4-year, accredited doctoral-level naturopathic medical schools. As of 2015, there are 17 US states, 2 US territories, and a number of provinces in Canada, Australia, and New Zealand that recognize licensure for NDs. The principles of naturopathy are as follows:

1. Holistic approach to patient care
2. Identification of underlying causes rather than symptomatic treatment
3. Use of therapy to promote the body's self-restorative powers
4. Emphasis on self-care and prevention
5. Interdisciplinary cooperation with other medical providers

Hypnosis

Hypnosis is a method of helping patients to move beyond conscious and subconscious blocks that may thwart their healing process. Under hypnosis, patients are active problem solvers who incorporate their moral and cultural ideas into their behavior while exhibiting a heightened responsiveness to the expectations expressed by the therapist [32]. This technique may be useful in such diverse situations as tobacco cessation, chronic pain, and irritable bowel syndrome.

Hypnosis is a collection of methods that can be carried out by a therapist or applied by self-methods. Although the process is mainly self-guided, most patients seek guidance from a therapist when seeking this treatment. This can be placed in the category of mind–body techniques, and it can be used to treat a variety of medical conditions.

The following are six main principles that are discussed by Dr. Steven Gurgevich in his *Hypnosis and House Call book* and DVD [33] (Table 8).

Table 8 Principles of hypnosis

Process involved in hypnosis	Description of process
Educate	Goal of this step to remove fear and to teach patient about the process of hypnosis
Tailor	This is when the practitioner is able to "tailor" the technique to participants unique needs and beliefs
Induce trance	The process of getting the participant to begin the hypnosis process; there are many ways this can be performed
Utilizing trance	The process of identifying and working on the problems that are the reasons that the participant sought this type of treatment
Re-alert	This step involves the reversal of the induction technique
Debrief	With the patient alert, there is a discussion regarding the process and next steps

There is a certification process to become certified in hypnotherapy. Currently certification and licensure are required in the following states: Colorado, Connecticut, Florida, and Washington. It is important that the practitioner also has a background in either the field of medicine, psychology, or social work. The American Society of Clinical Hypnosis (ASCH) is recognized as the organization that provides the training and education needed for a practitioner to obtain this certification. Although there are many studies that have been done in the field of hypnosis research, outcomes have had varying levels of success [33].

Biofeedback

This technique has been used since the mid-twentieth century and is used in an attempt to improve movement patterns for chronic illness or after injuries. The positive part of the treatment is that the patient is able to be given information on how to improve their condition during their sessions so that they can attempt to manage these conditions/problems better in the future.

Biofeedback training is used to assist patients and clinicians during rehabilitation. There is no formal licensure process that is required; but

certification exists. There are two types of biofeedback: physiological biofeedback and biomechanical biofeedback. Most of the research in this field focuses on the use of biofeedback in rehabilitation of patients with neurological disorders. EMG biofeedback is the most popular form of biofeedback. The evidence to support the use of biofeedback in rehabilitation appears promising; however, there is a lack of systematic reviews including a large number of RCTs examining this subject [34].

Feldenkrais Technique

Feldenkrais is a technique that was developed by Dr. Moshe Feldenkrais in the 1950s. He was trained a chemist and neurophysiologist. After having his own problems with knee pain, he studied and developed his method [35]. The Feldenkrais method can be done as a group or individually. The group lessons focus on one being aware of one's movements, and the practitioner leads participants through a sequence of movements. Even though the class is in a group setting, participants go at their own pace, and the process does not involve modeling a central instructor. The goal of the treatment is to identify and reeducate the mind and body and to essentially unlearn physical dysfunctions by using proper movements. Most sessions are between 30 and 60 min. The role of the Certified Feldenkrais Practitioner (CFP) is to direct attention to habitual movement patterns that are inefficient or strained. Then the CFP can teach the patient new patterns using gentle, slow, repeated movements that can be both active and passive in nature.

There is limited scientific evidence on the effectiveness of the Feldenkrais technique. To teach this technique, there is a certification process. Licensure is not needed, but to obtain the qualification of Certified Feldenkrais Practitioner (CFP), Feldenkrais teachers complete close to 1000 h of training. It is training that physical therapists commonly study to add to their approach when treating conditions that involve pain and movement dysfunctions.

Conclusion

Integrative medicine is a diverse collection of practices, procedures, and philosophies of healing. There is widespread use of IM, and there have been improvements in the scientific studies to confirm that these practices are safe and effective. Physicians should be aware of the IM practices used by their patients and work to become knowledgeable in the legitimate uses of alternative medicine. Physicians should remain open to discussion of IM with patients and assist them in selecting IM practices and practitioners that have demonstrated effectiveness and safety.

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Family Medicine
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The Family Physician's Role in a Changing Health Care System

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Definition/Background

Primary care is at a crossroads. Our current delivery systems are unsustainable and lack the resiliency to survive in new environments where total cost of care, patient experience, and patient-centered outcomes are the primary determinants of success. In order for primary care to remain relevant and viable, new solutions must be created and new roles must be defined that are practical and transformative. These new roles and solutions must provide clear value with highly satisfying services that both meet the needs of the patient and provide for population health. Family medicine also must consider the ways in which care coordination can be improved. This is especially important in managing populations and subpopulations of patients with multiple chronic conditions. The cost of care must come down and quality must remain high in order to be able to deliver affordable care.

Family physicians have traditionally seen our value in maintaining a longitudinal provider-patient relationship. The historical value of primary care is the ability to form relationships with patients to provide proactive and timely care, avoiding costly inpatient hospital stays and tests. Recent studies have shown that when patients have access to primary care, there are fewer ER visits, hospital admissions, and lower overall cost of care with improved outcomes and quality of life [1]. However, regulatory and payment changes that started nearly a decade ago are now gaining momentum and will have significant impact on the ability of primary care providers to maintain this same depth of relationships with all of our patients. More people will now have access to health insurance, and because of this there will be increasing demand on a shrinking pool of primary care providers. Widely cited research shows that to accomplish all the necessary preventive services for the current average panel size would take 27 h a day. And yet, because the work necessary to keep people healthy is often not valued, increasingly family medicine practices have shifted to treating acute illnesses while long-term health goals may be deferred to maintain higher and higher volumes and productivity. Recent work has begun to redesign the models of primary care, aimed at allowing patients to have highly satisfying experiences with physicians who also remain fulfilled and happy in their careers.

It is clear that the healthcare system in the United States is changing. Because of this, the specialty of family medicine has a choice to make: redefine our roles to make us an essential and valuable part of this system or cling to outdated roles and risk irrelevancy.

The History of the Family Physician

The specialty of family medicine began as a reaction to a vacuum where there was an absence of continuous lifelong care that acknowledged the needs of individuals as part of a family, a community, and a society. This role evolved to become the symbol of a physician within communities and who was the expert who defined health in an individual's life.

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The formal concept of primary care originated in post-World War I Europe, where there was heavy demand for healthcare in an environment of minimal resources. The explicit description of a primary or general medical service as distinct from specialty care was first described in the Dawson report, published in Great Britain in 1920. This report describes a community-based physician who was responsible for leading a team that was tasked with maintaining the population's health- an ideal that we are starting to return to after almost 100 years [2]. It was not until 25 years later that primary care became the foundation of the health system of the United Kingdom, where 80 % of patients' interaction with healthcare is in the primary care arena [1].

Profound changes in twentieth century economies and demographics continued to have a significant impact on the practice of medicine. In the United States, the rapid expansion of the health insurance system led to a large influx of funding into the healthcare system. This allowed investment to improve and expand medical education and postgraduate training. These dual forces had the effect of increasing the number of physicians in the workforce while simultaneously attracting them to higher-paying specialty practices [3]. These changes in the healthcare workforce were not followed by changes in the consumption of healthcare, which continued to be driven largely by community-based primary care outside the walls of the new tertiary and quaternary academic medical centers. By the 1950s, the movement toward specialty care had progressed far enough to prompt the American Medical Association to call for a special effort to ensure the preservation of the generalist physician [3]. The first formal general practice residency programs were established in the 1960s, and the American Academy of Family Physicians was formally launched in 1971 [4].

In 1978, the World Health Organization (WHO) convened the first International Conference on Primary Health Care and defined primary care as

> . . .essential health care based on practical, scientifically sound and socially acceptable methods and technology made universally accessible to individuals and families in the community through their full participation and at a cost that the community and the country can afford. . .It forms an integral part of both the country's health system, of which it is the central function and main focus, and the overall social economic development of the community. It is the first level of contact for individuals, the family and the community. . .and constitutes the first element of continuing health care process [1].

As time has passed, we have learned more about the value of primary care and the essential features of high-quality care. As a result of this, the WHO updated the definition of primary care in 2008 to include comprehensive care, team-based care, integration into the community, and a special focus on prevention and health promotion [1]. Since it is a specialty that responds to the needs of the communities it serves, the role of the family physician will continue to evolve. The current role is probably best described as providing care that is based on "knowledge of the patient in the context of family and community that emphasizes disease prevention and health promotion" [5].

Up until very recently, Family Medicine physicians in the United States have been governed by a fee-for-service model. Practices were seen as successful based on visit volume and revenue in a system that perversely rewarded clinics when patients were sick rather than healthy. These incentives flew directly in the face of the philosophy and ethics of the profession leaving providers with a difficult dilemma: create a practice that is true to the values of Family Medicine or increase visits and volumes to survive financially.

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Market and Other Forces that Necessitate Changing the Role of the Family Physician

While providers have traditionally been held accountable to volume targets with revenue tied to how sick rather than healthy the patient is, changes in healthcare are quickly pushing Family Medicine, and all of primary care, to focus on health promotion instead of sick care.

In 2012, healthcare spending in the United States accounted for 16.9 % of gross domestic product (GDP), the highest percentage among OECD (Organisation for Economic Co-operation and Development) countries and more than 7 % higher than the OECD average [6]. The United States per capita spending in 2009 was $8,160, and the Center for Medicare and Medicaid Services (CMS) projects by 2018 per capita spending will be over $13,000 [7, 8]. Despite this extra spending, life expectancy in the United States is 1½ years less than the OECD average, and the gap between life expectancy in the United States and other OECD countries is increasing [6]. One of the reasons cited for the slower progress in life expectancy is a gap in primary care [6].

In contrast to the situation in the United States, countries that place a stronger emphasis on primary care as a promoter of health as opposed to being reactionary to illness demonstrate less health care spending per capita with improved outcomes. Spain adopted a national health system in 1986 and, with a primary care physician-to-population ratio similar to that of the United States, was able to lower health spending to 8.4 % of their GDP while demonstrating improved overall health [1]. Examples from other countries demonstrate that strong primary care with enhanced accessibility improves health outcomes, reduces hospital use, improves equity, and slows rates of cost growth for medical services. Countries such as Holland and the United Kingdom have further strengthened primary care by exempting practices from deductibles and cost sharing, by providing support for after-hours care and by providing monetary incentives to the primary care practices that support ready access to care and the formation of teams [9].

In the United States, society, the government, and healthcare payers have come to the conclusion that spending 1 out of every 3 tax dollars on health care is not sustainable for our nation [1]. The Institute for Healthcare Improvement (IHI) has attempted to address these issues with the development of the triple aim initiative, which focuses on increasing the quality of care, decreasing the total cost of care, and improving health outcomes for individuals and populations [10, 11]. This creates a new consumer focus and accountability that medicine, especially family medicine, must respond to. In addition, the Affordable Care Act (ACA) will expand healthcare insurance coverage to individuals who have likely not been regular utilizers of primary care services [12]. These two forces will have the effect of increasing the demand on primary care services while simultaneously increasing the accountability for the outcomes and value of these services.

In terms of payment reform, to date there have been three major payment models that have emerged as viable methods to address consumer and payer demands and have begun the stepwise process of evolution toward a total cost of care or population-based payment model. The first is value-based purchasing, increasingly used by Medicare, which is a pay-for-performance program that incentivizes provider performance in achieving predetermined measures of both process and outcome. By creating connections between reimbursement and outcomes, this payment model shifts the focus to the quality of healthcare and patient experience. Projections suggest that Medicare's value-based purchasing programs will continue to reduce the relative weight of clinical processes in reimbursement models while increasing the weight of outcomes and efficiency [13]. The second major model is the "bundled payment" system, wherein the payer disburses a single payment to cover an entire episode of care. Providers stand to gain in this payment model if they can provide the care for less than the proposed payment. The third major type of new payment model to emerge is the Accountable Care Organization (ACO), which refers to a network of affiliated providers who accept collective accountability for the total cost of care and the quality of that

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care for a defined population of patients. The purpose of ACOs is to reward providers for controlling or reducing the total cost of care through services that focus on prevention, care coordination, chronic condition management, palliative care, as well as patient and community engagement. In 2014, 67 % of the US population was living in a service area with at least one ACO, and 5.3 million Medicare beneficiaries were treated by an ACO [13].

Another important emerging market force that is currently affecting the evolution of primary care is the rapidly increasing shift toward consumerism in healthcare. As a result of changes in the insurance marketplace, more people have access to healthcare, and the relative share of personal responsibility for healthcare expenses is increasing. Trends in the marketplace are demonstrating that people are choosing leaner or higher deductible plans, effectively increasing their out-of-pocket expenses. With more of their own money at stake, patients are applying their comparison shopping savvy to healthcare choices and are looking for providers that can offer clear value, convenience, and new options for access. In some cases, prospective patients are ranking convenience and affordability far above continuity of care in their choice of provider [13].

A Proposed Model: Offering a Path to Innovation

In order to respond to these new market drivers and meet the needs of the patient as a consumer, healthcare organizations are beginning to apply this consumer lens to primary care and are discovering that consumers understand primary care as being divided into four distinct domains: Self-Care, Assessment/Detection, Treatment, and Management. Several successful systems are implementing a team-based model of care built around these four patient-focused domains.

The four domains can be envisioned as a continuum that patients move back and forth within while primary care seeks to provide the most appropriate service at the right time and place. The goal is to help individuals remain in the Self-Care domain autonomously with only infrequent intervention from the clinic or to help the patient regain the capacity to return to the Self-Care domain. This means the healthcare system will at times need to offer support and information in a different, less intensive, and possibly more effective way.

Currently, primary care spends significant time and energy in the Self-Care domain doing things to patients that are better suited to less intensive modes of care. Certain activities such as wellness exams and follow-up for healthy individuals with no risk factors may help to ensure continued assessment of risk factors and to sustain revenue streams. This is not intended to imply that primary care does not engage patients in the Self-Care domain; instead it implies that our current process may be inappropriate for effectively serving this patient population and that service offerings must be adjusted to meet the appropriate needs of our patients based on their clinical, social, and behavioral risk factors.

Systems such as Geisinger Health System, Kaiser Permanente, Group Health Cooperative, the Military Health System, the Mayo Clinic, and the national health services of several European countries have adopted a team-based care model as a way to meet patient needs in these four domains [14]. Team-based care models are also a positive way to respond to the needs of population health models, with their associated influx of data-driven care needs. However, the adoption of a team-based care model is often hampered by the persistence of fee-for-service reimbursement models, leaving physicians reluctant to delegate work to others or to consider nonvisit care options [14].

Key Characteristics of Ideal Family Physician of the Future

The ideal family physician of the future is the leader of a team but not necessarily always in charge. The ideal family physician understands their team, enables everyone to work at the top of licensure in support

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of patient health, and is acutely aware of their value and skill set within the team. The ideal family physician cares for patients as a member of the team that extends beyond the clinic proper to all of those who touch the patient in a healthcare capacity.

While the specialty must continue to evolve to meet the needs of the communities it serves, there are four key characteristics of the family physician that will be crucial for the future of the specialty.

First, family physicians must be advocates for understanding the true needs of the population of patients we serve. Patients' needs must be the driving force for any changes in our healthcare delivery systems. Although family physicians are often closer to our patients than physicians in other specialties, we cannot make the mistake of assuming that we know what our patients need. For instance, family physicians often indicate that our patients' deciding factor in choosing a primary care provider is continuity. However, patients are more likely to rank access, affordability, and convenience higher than continuity [13]. Understanding the true needs of our patients may lead to very different healthcare delivery systems than the ones we currently have. However, it is usually not sufficient to simply ask patients what they want or need. Like consumers in other industries, patients may not know or are not able to express their latent desires. So asking a patient advisory council for input or sending out patient surveys may not lead to the most innovative or transformative outcome. The family physician needs to be an advocate for utilizing the tools and skills that other service industries have used in order to successfully understand patient needs.

Second, the family physician needs to be a champion for change. For the foreseeable future, change is likely to be the only constant in many healthcare organizations. As advocates for the true needs and voice of the patient, family physicians can help shepherd their organizations through the requisite changes that will need to happen in response to healthcare reform. Our clinics and care teams will look to the physicians to champion the changes that will be necessary to allow family medicine to continue providing high-quality and high-value care.

Third, the family physician needs to be a care team leader. While often this is interpreted as being in charge of the care team, being a leader is much different. Care team leaders will be responsible for ensuring that populations of patients are getting evidence-based preventive services and chronic condition management through the most efficient and cost-effective methods possible. Care team leaders work with the patient and their family to diagnose a problem and then create an anticipatory treatment plan that can be executed by other team members. When a patient needs to be seen in the clinic, a care team leader ensures the patient is paired with the team member whose licensure most closely matches the patient's needs. Care team leaders remember to respect the patient and their relationship with the provider by taking the first few minutes of the visit to introduce the new team member and explain why they are the best care provider to meet the patient's needs. This reassures the patient that their family physician is still overseeing their care and gives the patient permission to engage with other team members. These warm handoffs never fail to soothe patient anxieties and may also help patients engage with new services that they would have otherwise been skeptical or apprehensive about. As the leader of the care team, physicians must provide the team with model collaborative and communicative behavior. The leader must demonstrate how to value each team member for their role and encourage the entire team to work at the top of their licensure in a way that benefits the patient. Excellent care team leaders support their team in a way that does not require direct oversight of each member's tasks but instead creates an environment of trust and collaboration that allows each team member to function autonomously and seamlessly within the group. In this way, it is also important for family physicians to participate in regular teaching to support their care team- remembering the adage that we are all teachers and we are all learners.

Lastly, family physicians will need to increase their depth of medical knowledge and skills to complement the impressive breadth of knowledge that they already possess. As both population demographics and the healthcare industry change, primary care will be expected to regularly care for the types of complex patients that were traditionally referred to specialty practices. Family physicians will need to

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become more comfortable in the management and coordination of complex chronic diseases that will increasingly be seen in the same patient, and often superimposed on significant social comorbidities. This type of management has not been within the scope of training for family physicians to date but should be considered as part of their future education. In order to help these patients, we must embrace the skills and talents of our team members and be comfortable in delegating care to the team member who has skills that are the most appropriate for the patient's needs. Like all members of the care team, family physicians must be prepared to do all the things we were trained to do and challenge ourselves every day. At times, for noncomplex patients this means stepping aside and allowing our teams to provide care when necessary. On the other hand, with complex patients this may mean that we need to stretch ourselves to provide high-quality care. Recognizing our full potential to make diagnoses, perform procedures, and manage complex chronic conditions is as important as understanding our limitations and reaching out and surrounding ourselves with trusted specialty partners when the need is beyond our training. Having trusted and collaborative relationships with specialty providers not only provides our patients with the highest quality of care but also allows us to learn through dialogue and cooperation. Being a family physician means being a member of a team. That team includes the formal care team of allied health staff and also the patient, their loved ones, and individuals we can go to with questions when we need support.

Conclusion

Family physicians have a clear value within society, and it is incumbent upon all of us to continue to demonstrate that value as the landscape shifts. The changing landscape provides us with a unique opportunity to reposition ourselves as a supportive force in maintaining health for our patients and the populations we care for. We can only survive as specialty if we understand how we can best fit within the changing ecosystem of healthcare. The future is bright for the family physician and the teams we support.

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Patient-Centered Medical Home

Ivan Abdouch

Contents

Definition of the Medical Home

While the most commonly used term is "patient-centered medical home," others such as "primary care medical home," "personal medical home," "advanced medical home," and "healthcare home" also exist. Despite variances among these concepts, all share similar core values and principles. Except for direct quotes that refer to a specific medical home, the term "medical home" will be used for this chapter in an effort to be more inclusive.

The fact that each state has its own definition for the medical home illustrates that no universal definition exists. The medical home is difficult to define because it is not a place or an object. It is a concept that is intended and designed to encourage primary care physicians to achieve excellence by focusing all aspects of healthcare delivery on the patient. It does so by including specific elements – patient-centered, comprehensive team-based, and coordinated care that is accessible and is committed to quality and safety.

Perhaps the closest thing to a definition from the family physician perspective is offered by the policy statement from the American Academy of Family Physicians (AAFP):

> The patient-centered medical home is a transition away from a model of symptom and illness based episodic care to a system of comprehensive coordinated primary care for children, youth and adults. Patient-centeredness refers to an ongoing, active partnership with a personal primary care physician

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> who leads a team of professionals dedicated to providing proactive, preventive and chronic care management through all stages of life. These personal physicians are responsible for the patient's coordination of care across all health care systems facilitated by registries, information technology, health information exchanges, and other means to ensure patients receive care when and where they need it. With a commitment to continuous quality improvement, care teams utilize evidence-based medicine and clinical decision support tools that guide decision making as well as ensure that patients and their families have the education and support to actively participate in their own care. Payment appropriately recognizes and incorporates the value of the care teams, non-direct patient care, and quality improvement provided in a patient-centered medical home. [1]

History of the Medical Home

While the medical home has gained recent attention, it is not a new entity and it did not suddenly appear. The original medical home concept was established by the American Academy of Pediatrics (AAP) in 1967, when it was designated to be one central source of a child's pediatric records, especially for children with special healthcare needs. The concept was expanded by the AAP in 2002 to include care that is accessible, continuous, comprehensive, family centered, coordinated, compassionate, and culturally effective [2]. Similar models were subsequently developed by the AAFP in 2004 [3] and the American College of Physicians (ACP) in 2006 [4]. This movement was influenced along the way by a number of events. Some of the key points include:

1978: The Declaration of Alma-Aita was introduced at the International Conference on Primary Health Care – the first international declaration of primary healthcare's key role in promoting the health of all people, subsequently supported by the World Health Organization [5].

1996: The Institute of Medicine (IOM) redefined primary care 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" [6].

2001: The IOM defined "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." – a statement of recognition that patients and families are core members of the care team, and the medical practice should provide what they need in order to be full partners in the process of their care [7].

2002: The Future of Family Medicine project began and recommended that health system change should "include taking steps to ensure that every American has a personal medical home [. . . and] developing reimbursement models to sustain family medicine and primary care" [3].

2005: Dr. Barbara Starfield published a very influential article called "Contribution of primary care to health systems and health" in which she identified six primary care mechanisms that benefit 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 [8].

Principles and Characteristics of Medical Homes

With the medical home's history, the Declaration of Alma-Aita, the IOM definition of primary care and patient-centered care established, and the identification of specific mechanisms to target, the medical home movement gained momentum, and it was determined that guidelines were needed.

In 2007 the AAFP, AAP, ACP, and American Osteopathic Association (AOA) developed the "Joint Principles of the Patient-Centered Medical Home," listing elements to include in a medical home [9]. While characteristics may vary among practices, the characteristics that determine medical home status are more uniform because of these Joint 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:

- 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.
- It should allow physicians to share in savings from reduced hospitalizations associated with physician-guided care management in the office setting.
- It should allow for additional payments for achieving measurable and continuous quality improvements.

These principles have provided some standardized assurances of what medical homes will provide – patient-centered, comprehensive team-based, coordinated care that is accessible and committed to quality and safety. The application and impact of these elements are illustrated in Fig. 1.

As such, the medical home:

- Is accountable for meeting the large majority of each patient's physical and mental healthcare needs – prevention and wellness, acute care, and chronic care. This requires a team of care providers that include physicians, physician assistants, advanced practice nurses, nurses, pharmacists, nutritionists, behavioral health providers, social workers, educators, and care coordinators. In cases where having these individuals present is not practical, the medical home can be "virtual teams" where physicians and their patients are connected with providers and services in their communities.
- Is responsible for actively coordinating all facets of each patient's care, guiding them through the sometimes complex maze of specialty care, hospitals, home healthcare, and community service. This is especially important during transitions between sites of care. This is enhanced by maintaining means of clear and open communication among patients and families, the medical home, and members of the care team.
- Provides a variety of means for patients to access services such as shorter waiting times for urgent needs, enhanced visit availability, continuous telephone or electronic access to a care team member, and nontraditional methods of communication such as e-mail and telephone care. Patient preferences regarding access should be honored.
- Consistently uses evidence-based medicine, clinical decision-support tools, shared decision-making with patients and families, continuous performance measurement and improvement, monitoring and responding to patient outcomes and satisfaction, and practicing population health management.

The Role of Family Medicine in the Medical Home

The Future of Family Medicine report states, "The development of family medicine and its identity as a discipline has been grounded in the core values of continuing, comprehensive, compassionate, and personal care provided within the context of family and community." Placing this next to the IOM definition of primary care makes family physicians ideal for serving as team leader in the physician-directed medical home as specified in the Joint Principles.

The USA spends more on healthcare than any other country in the world, yet the life expectancy in the USA is no greater than most other countries that spend far less (see Fig. 2). The reason for this has been the subject of considerable study.

It has been proposed by many that a major contributor to these differences is the proportion of primary care to specialty care in the health system, i.e., systems with a higher primary care to specialty care ratio produce better outcomes at a lower cost. Evidence supports this proposal [8, 10–12].

Medicare claims data indicate that the more generalists per capita, the lower the costs and the better the quality of care (see Fig. 3), and, conversely, the more specialists per capita, the higher the costs and the lower the quality of care (see Fig. 4).

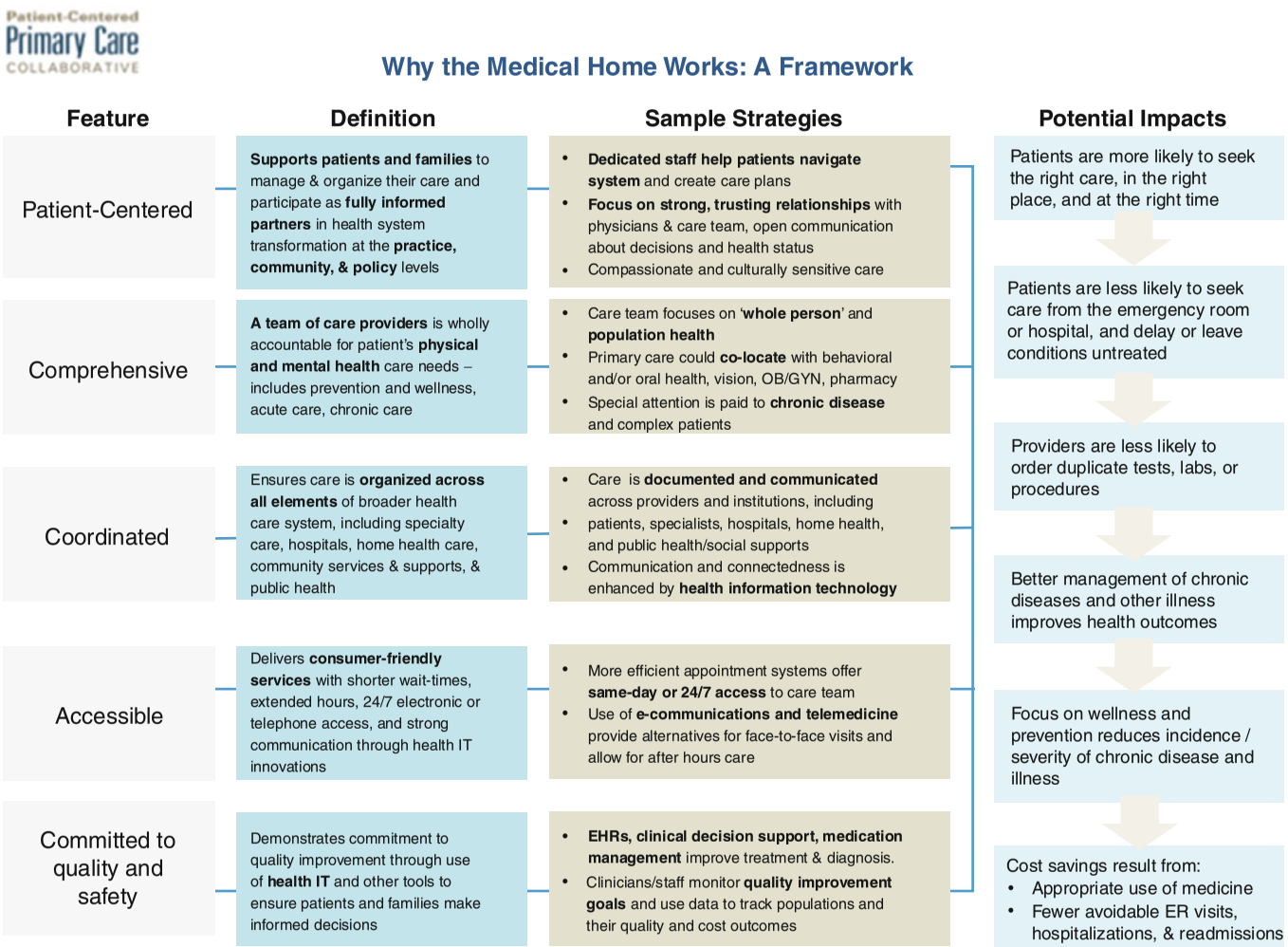


Fig. 1 Why the medical home works: a framework

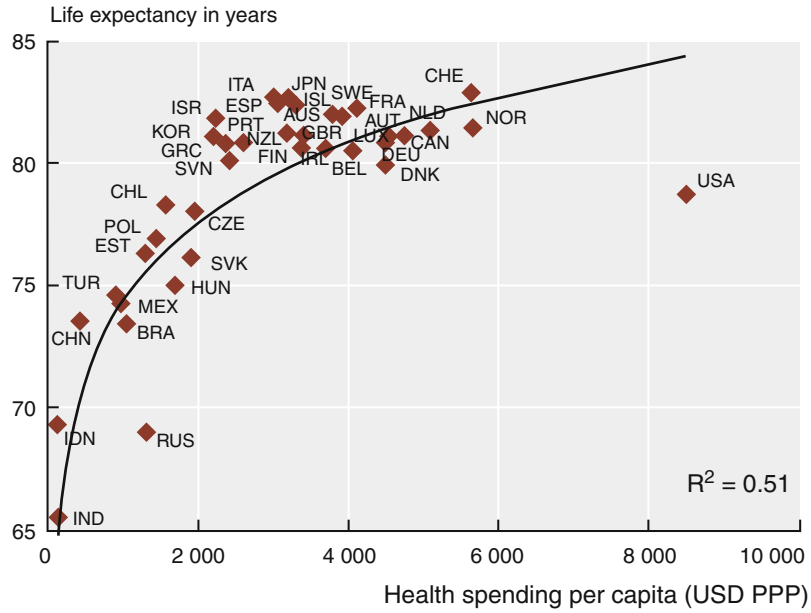


Fig. 2 Comparison among countries showing that the USA spends far more than all other countries with no gain in life expectancy over most other countries who spend far less

Studies conducted by Dr. Barbara Starfield demonstrated significant benefits of primary care [8, 10]. Examples include:

- Locations with stronger primary care systems in place have improved health outcomes over those with lesser primary care for all-cause mortality, cancer, heart disease, stroke, infant mortality; low birth weight; life expectancy; and self-rated health.
- Pooled results for all-cause mortality suggest that an increase of one primary care physician per 10,000 population was associated with an average mortality reduction of 5.3 % or 49 per 100,000 per year.
- An increase of just one primary care physician yields 1.44 fewer deaths per 10,000 persons.
- Adults with a primary care physician rather than some other specialist had 33 % lower costs of care and were 19 % less likely to die (after adjusting for demographic and health characteristics).

Despite the demonstrated benefits of primary care, the supply of primary care physicians in general and family physicians in particular remains very low (see Fig. 5), creating a difficult barrier to improving the performance of healthcare in the USA.

Role of the PCMH in the Health System

As the PCMH model has continued to develop, the healthcare system has seen its value and the concept has begun to be incorporated into other arenas.

One instance of this is the role of the medical home in Accountable Care Organizations (ACOs) [13]. The Centers for Medicare and Medicaid Services (CMS) define ACOs as "groups of doctors, hospitals, and other health care providers, who come together voluntarily to give coordinated high quality care to their Medicare patients" whose goal is "…to ensure that patients, especially the chronically ill, get the right care at the right time, while avoiding unnecessary duplication of services and preventing medical errors." [14] This purpose of improving quality of care, improving outcomes, improving efficiency, and reducing health costs for defined populations bears a striking resemblance to the purposes of the medical home. CMS requires ACOs to maintain a strong network of primary care providers,

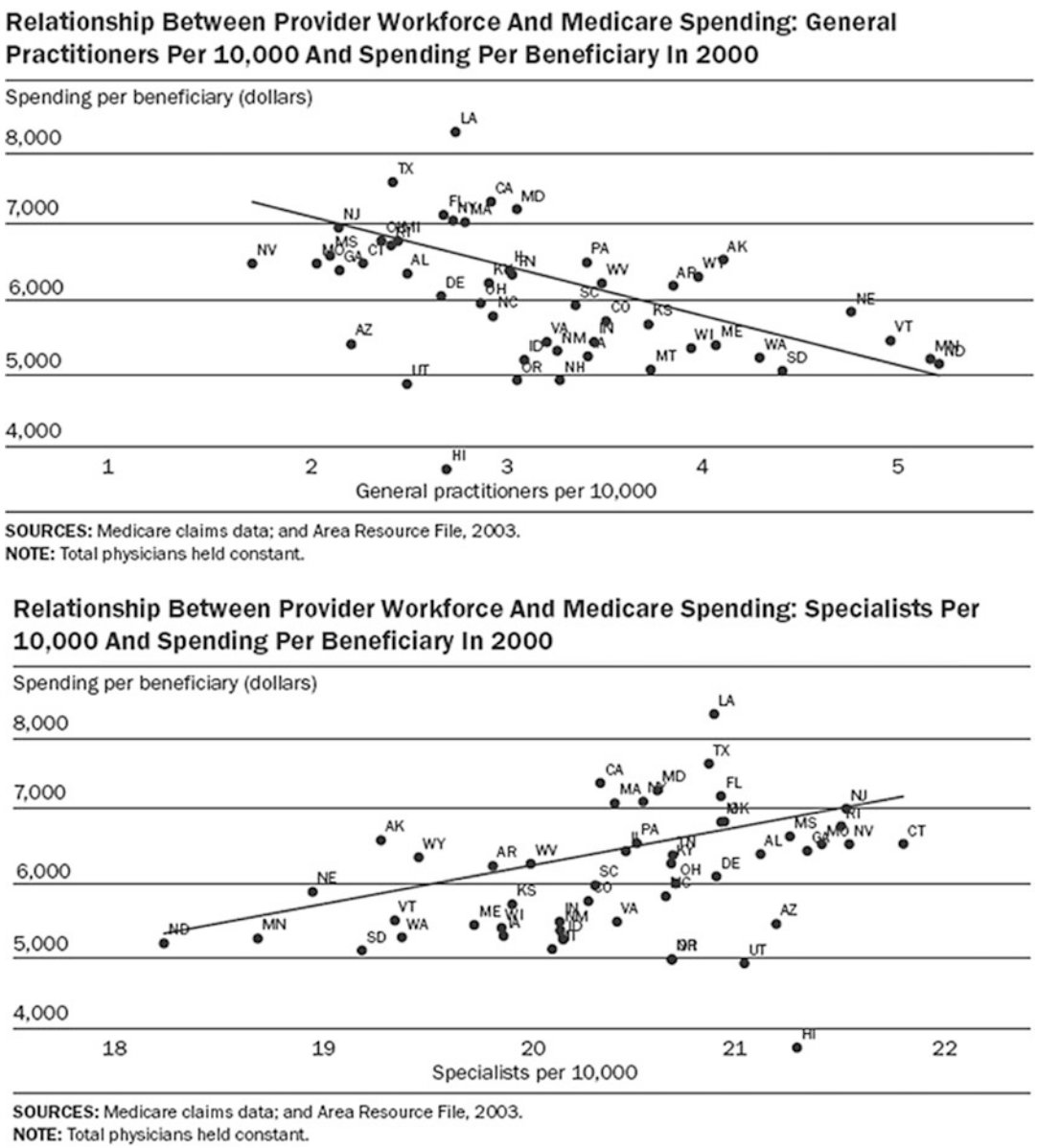
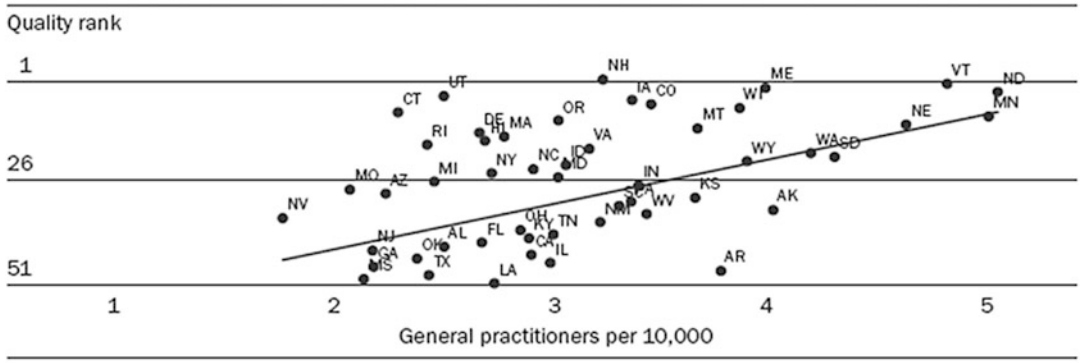


Fig. 3 The cost of care decreases as the supply of generalists per 10,000 population increases, and the cost of care increases as the supply of specialists per 10,000 population increases

but not specifically medical homes. However, it has been suggested that ACO performance can be improved through application of medical home methods along with innovative payment models in which all participating clinicians are rewarded for improving care delivery and health outcomes, and patients are rewarded for making healthy choices. In so doing, all of the benefits of the medical home would be extended throughout the ACO's population. CMS data suggest that this approach has at least initially resulted in improved cost-effectiveness of care and received shared savings.

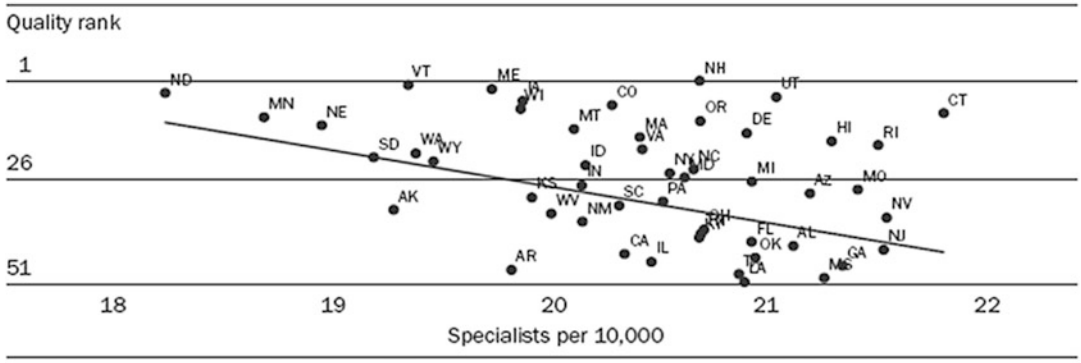
Another proposed role for the medical home is in the "medical neighborhood" [15]. Like the medical home, this is a concept for which there

Relationship Between Provider Workforce And Quality: General Practitioners Per 10,000 And Quality Rank In 2000



SOURCES: Medicare claims data; and Area Resource File, 2003.
NOTES: For quality ranking, smaller values equal higher quality. Total physicians held constant.

Relationship Between Provider Workforce And Quality: Specialists Per 10,000 And Quality Rank In 2000



SOURCES: Medicare claims data; and Area Resource File, 2003.
NOTES: For quality ranking, smaller values equal higher quality. Total physicians held constant.

Fig. 4 The quality of care increases as the supply of generalists per 10,000 population increases, and the quality of care diminishes as the supply of specialists per 10,000 population increases

is no universal definition, but it has been described by the Agency for Healthcare Research and Quality (AHRQ) as "a PCMH and the constellation of other clinicians providing health care services to patients within it, along with community and social service organizations and State and local public health agencies." The "neighborhood" includes all forms of ambulatory care, diagnostic services, pharmacy, acute and post-acute care facilities, community/social services, and state/local public health entities, with the medical home serving as the central point of contact for the patient and the primary coordinator of the patient's care across various neighbors. AHRQ's outcome statement says, "The intended outcomes of a high-functioning medical neighborhood include improved patient outcomes; patient safety; patient experience; and possibly lower costs through reduced duplication of services, increased delivery of preventive services, and more evidence-based patient care (resulting in fewer readmissions, polypharmacy issues, and adverse events, for example)."

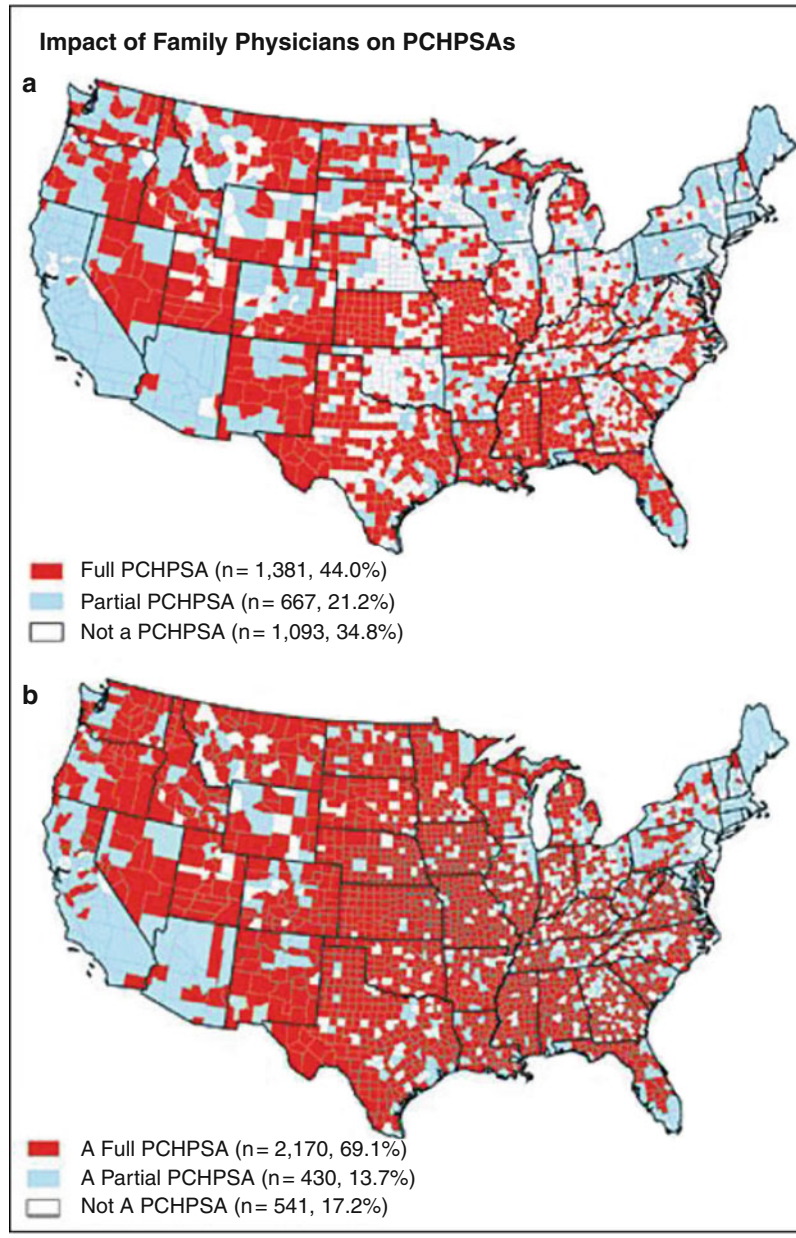


Fig. 5 Map A demonstrates counties designated as Primary Care Health Personnel Shortage Areas (*PCHPSA*); Map B demonstrates counties that would be designated as PCHPSA if family physicians did not practice in those counties

Results and Evidence

The medical home model has been implemented nationwide by a growing number of clinical practices and clinics of all sizes, state and federal agencies, health plans, and employers. As the number of medical homes has expanded, the pool of data assessing outcomes is growing [16–22]. And while the areas impacted vary among medical homes, the general trend has been a demonstration of value added by this model for patients of all ages and in a variety of settings.

An evaluation of aggregated outcomes from 28 peer-reviewed studies, state government program evaluations, and industry reports during

2013–2014 revealed that 24 found improvements in utilization, 17 found improvements in cost, 11 found improvements in quality, 10 found improvements in access, and 8 found improvements in satisfaction.

Examples of outcomes documented by various peer-reviewed articles and industry reports include 31–50 % fewer urgent care and emergency room (ER) visits, 21–53 % fewer hospital admissions, 15–50 % fewer hospital readmissions, 15–40 % fewer inpatient stays, 21 % reduction in inpatient services, 65 % reduction in specialist utilization, 18–65 % improvements in medication management, 31 % increase in self-management of blood sugar, 18 % lower healthcare claims costs, 7 % lower cumulative total spending, and appointment wait time reduced from 26 days to 1 day.

Public statements in support of the medical home have come from the President of the USA, Senators from both parties, the National Academy for State Health Policy, patient and consumer groups, health quality organizations, physicians and providers, purchasers, health plans, pharmaceutical firms, and various think tanks.

Certification, Recognition, and Accreditation

The release and widespread acceptance of the Joint Principles of the Patient-Centered Medical Home in 2007 launched a primary care redesign movement across the country. In view of this, the need for establishing entities offering medical home recognition or accreditation was recognized. In response to this need, AAFP, AAP, ACP, and AOA developed the following "Guidelines for Patient-Centered Medical Home Recognition and Accreditation Programs" [23] to act as a standard for this process, specifying that all Patient-Centered Medical Home Recognition or 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

Accreditation is not required to become a medical home, but some individual entities mandate completion of an accreditation or recognition program for their purposes. Therefore it is important to determine whether such a requirement exists when an agreement is being considered between the practice and another entity – e.g., ACO, payment incentive program, federal grant, and major practice payer agreements.

At the time of this writing, four separate certifying agencies exist – the National Committee for Quality Assurance (NCQA), URAC (formerly the Utilization Review Accreditation Commission), the Joint Commission, and Accreditation Association for Ambulatory Health Care (AAAHC). Each has its own characteristics and methods for applying the features of the medical home, but all comply with the "Guidelines for Patient-Centered Medical Home Recognition and Accreditation Programs." Additional recognition and accrediting agencies may be established as time passes.

RESOURCES	
AAFP PCMH Planner	http://www.aafp.org/practice-management/transformation/pcmh/planner.html
Family Practice Management	http://www.aafp.org/journals/fpm/explore/topic/pcmh.html
Patient-Centered Primary Care Collaborative	http://www.pcpcc.org
TransforMed	http://www.transformed.com/index.cfm
AHRQ Patient Centered Medical Home Resource Center	http://pcmh.ahrq.gov
NCQA Patient-Centered Medical Home Recognition	http://www.ncqa.org/Programs/Recognition/Practices/PatientCenteredMedicalHomePCMH.aspx
Joint Commission: Primary Care Medical Home	http://www.jointcommission.org/accreditation/pchi.aspx
URAC	https://www.urac.org
AAAHC	http://www.aaahc.org

Fig. 6 A few resources that provide information, tools, practice, self-assessment, and help with implementation

Practice Transformation

The transformation of a practice to a medical home is not without its challenges [24–26]. It is a gradual and tedious process that requires patience, diligence, tenacity, cooperation, commitment, and effective communication between the practice and the patient, among members of the practice, and between the practice and the community. There are many helpful resources available that provide information, tools, practice, self-assessment, and help with implementation. A few of these resources are listed in Fig. 6.

In Context

The medical home may or may not be "the" solution, but at a minimum it is certainly a worthy effort to reverse negative trends in medicine and at least something to build on. Many practices have reported that the valuable benefits from this process have been well worth the effort.

During transformation, however, caution must be exercised to not be distracted from the primary focus – the patient. In spite of the medical home's mantra of "patient-centeredness," physicians and practices are at risk of becoming so focused on all of the elements and metrics that they can and sometimes do lose sight of the most precious of treasures in primary care – the relationship between the patient and the physician. Every step of the way, the relationship should be assessed to make sure it is preserved and healthy. No aspect of the medical home should ever be allowed to take priority over that relationship.

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Family Medicine
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Chronology: The Evolution of Family Medicine as a Specialty in the United States

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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
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”

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Year	Event	Significance
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
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

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Year	Event	Significance
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
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 certified by ABFP (26,500 ABFP diplomates)	Most general practitioners had 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

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Year	Event	Significance
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 healthcare 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 organization
1994	Publication of *Family Medicine: Principles and Practice,* 4th edition (Taylor, editor; David, Johnson, Phillips, Scherger, associate editors)	Emphasis on core problems in clinical family medicine
	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

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Year	Event	Significance
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 healthcare 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 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 healthcare 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

(*continued*)

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Year	Event	Significance
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 healthcare 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
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 first edition published both in digital and print media

Medical Informatics, the Internet, and Telemedicine

Michael D. Hagen

Contents

Information systems and technology have become all-pervasive in the family medicine practice realm: electronic health records (EHRs), digital imaging systems, computerized physician order entry (CPOE) systems, decision support tools, billing, and evaluation and management (E&M) coding systems reside in nearly all family physicians' practices. Indeed, the vast majority of family physicians now use some form of EHR [1]. This chapter will focus on those aspects of clinical informatics most important to family physicians' effective use of information technology.

Electronic Records

Until the latter twentieth century, most physicians relied on paper records to store and maintain summaries of interactions with their patients. While such records served to support the care of individual patients in individual practice contexts, they did not afford efficient data extraction for communication with other providers or conduct of research. The rise of minicomputers and personal computers in the latter twentieth century provided the technical platforms for creation of electronic systems that could record, store, maintain, sort, and communicate information needed for patient care and development of new information [2]. Indeed, family physicians have adopted electronic health records at a steadily increasing pace [1] (Fig. 1).

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ELECTRONIC HEALTH RECORD ADOPTION

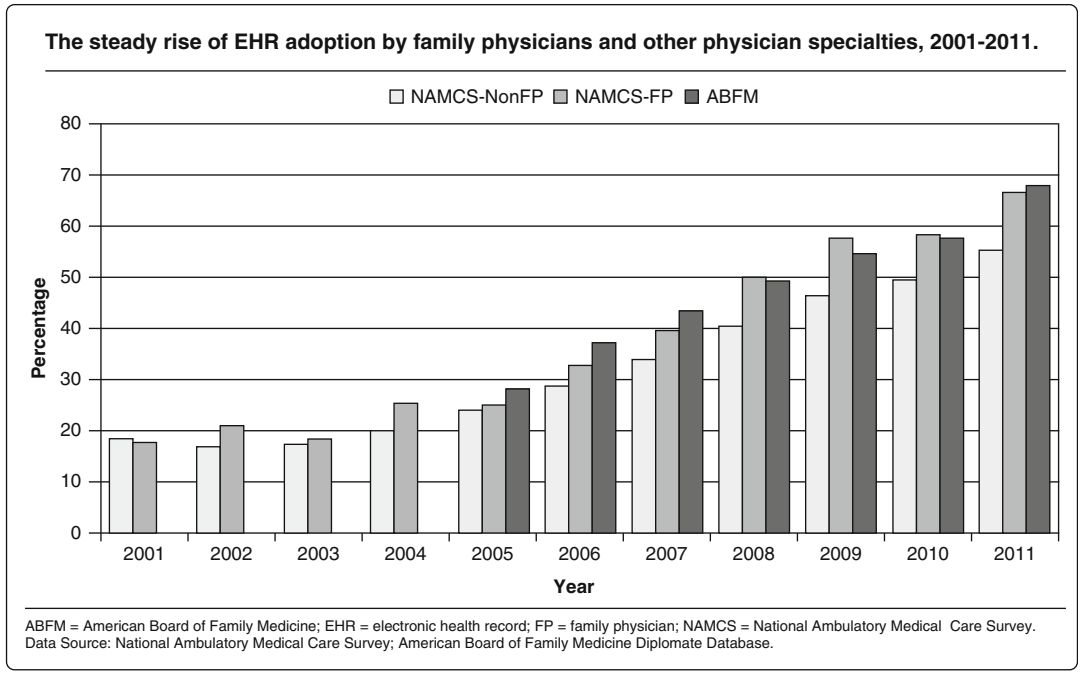
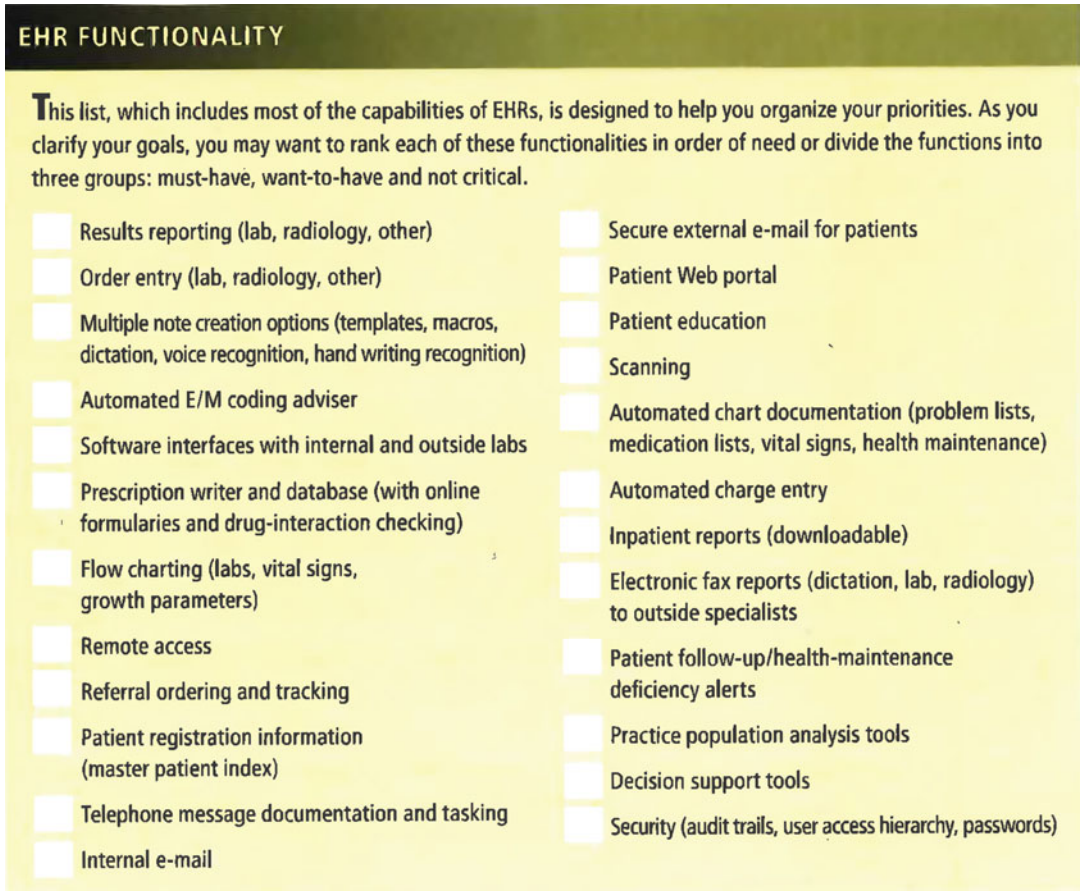


Fig. 1 EHR adoption rate for family physicians and other physician specialties, 2001–2011 (From: Xierali et al. [1]. Request for reprint submitted)

Family physicians face a multitude of options when attempting to select an EHR system appropriate to their particular practice contexts [3]. Costs, knowledge needed to use the system, and technological considerations can all complicate the decision process. Fortunately, tools exist to aid family physicians in making these decisions. The American Academy of Family Physicians (AAFP) has published protocols that family physicians can use to guide them in the selection process [4]. The AAFP describes multiple steps in making a selection: identify the decision-makers in the practice, clarify the goals the practice or organization hopes to accomplish in adopting an EHR, develop a request for proposals (RFP) that reflects your organization's needs, identify the vendors to which one should send the RFP, review the subsequent proposals and narrow the candidates to those that most closely meet your needs, attend demonstrations, seek out other users for their perspectives, rank the candidate vendors, visit sites that have the candidate systems in place, select a finalist, confirm your organization's commitment, and, finally, negotiate a contract (Fig. 2 (Functionality), Fig. 3 (RFP outline), Fig. 4 (Demo form), Fig. 5 (Vendor rating tool) [4]). The multiplicity of EHR vendors requires that family physicians take such a systematic approach to selecting the system that will work best for their practices.

Cost represents a substantial barrier to EHR adoption and maintenance [3]. As a means to promote EHR adoption, the HITECH Act of 2009 (part of the American Recovery and Reinvestment Act, the "stimulus bill") created several incentive programs [5]. These include incentives for meaningful use [6] and for participating in the Physician Quality Reporting System (PQRS) [7].

The PQRS has provided bonus payments for eligible physicians based on a percentage of Medicare part B billings. Participants can submit information either from claims data or by entering



EHR FUNCTIONALITY

This list, which includes most of the capabilities of EHRs, is designed to help you organize your priorities. As you clarify your goals, you may want to rank each of these functionalities in order of need or divide the functions into three groups: must-have, want-to-have and not critical.

- Results reporting (lab, radiology, other)
- Order entry (lab, radiology, other)
- Multiple note creation options (templates, macros, dictation, voice recognition, hand writing recognition)
- Automated E/M coding adviser
- Software interfaces with internal and outside labs
- Prescription writer and database (with online formularies and drug-interaction checking)
- Flow charting (labs, vital signs, growth parameters)
- Remote access
- Referral ordering and tracking
- Patient registration information (master patient index)
- Telephone message documentation and tasking
- Internal e-mail
- Secure external e-mail for patients
- Patient Web portal
- Patient education
- Scanning
- Automated chart documentation (problem lists, medication lists, vital signs, health maintenance)
- Automated charge entry
- Inpatient reports (downloadable)
- Electronic fax reports (dictation, lab, radiology) to outside specialists
- Patient follow-up/health-maintenance deficiency alerts
- Practice population analysis tools
- Decision support tools
- Security (audit trails, user access hierarchy, passwords)

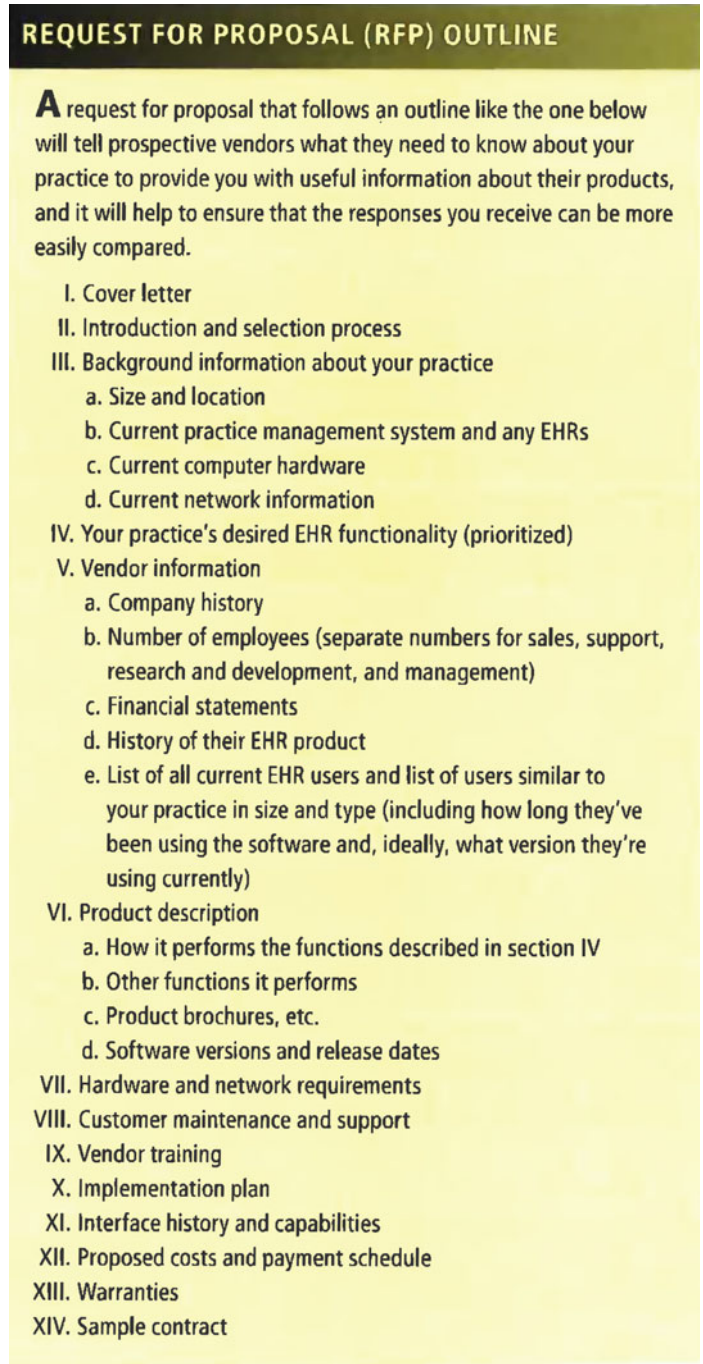
Fig. 2 Specification of EHR functionality (From: Adler [4]. Request for reprint submitted)

patient measures data via an approved registry (the American Board of Family Medicine (ABFM) has operated an approved registry since the program's inception; details available at the ABFM website, www.theabfm.org [8]). Beginning in 2015, physicians who do not participate in the PQRS will begin to experience adjustments (decrements) in their Medicare part B payments.

As noted, the HITECH Act also implemented incentives for adopting EHR technology. This incentive can total as much as nearly $44,000 but varies depending on when the professional enters the program [9] (Table 1). Additionally, the incentives differ depending on whether the professional chooses to participate via Medicare part B or Medicaid billings. To qualify for these incentives, physicians must use certified EHRs [10] and demonstrate meaningful use of these tools [6]. Generally, qualifying for meaningful use requires that the professional demonstrate and/or attest to the ability to perform particular operations in the EHR (e.g., computerized submission of prescriptions to pharmacies and collection and submission of quality measure data.) The Centers for Medicare and Medicaid Services (CMS) have issued frequent changes and updates to the regulations, so eligible professionals (physicians) should consult the CMS website/s for up-to-date information [6].

Although family physicians have adopted EHR systems at an increasing rate [11], many users continue to find frustrations with their systems [12]. Users find the systems cumbersome to use, difficult to navigate, and distracting in the

Fig. 3 Outline for a request for proposals (From: Adler [4]. Request for reprint submitted)



REQUEST FOR PROPOSAL (RFP) OUTLINE

A request for proposal that follows an outline like the one below will tell prospective vendors what they need to know about your practice to provide you with useful information about their products, and it will help to ensure that the responses you receive can be more easily compared.

I. Cover letter
II. Introduction and selection process
III. Background information about your practice
  a. Size and location
  b. Current practice management system and any EHRs
  c. Current computer hardware
  d. Current network information
IV. Your practice's desired EHR functionality (prioritized)
V. Vendor information
  a. Company history
  b. Number of employees (separate numbers for sales, support, research and development, and management)
  c. Financial statements
  d. History of their EHR product
  e. List of all current EHR users and list of users similar to your practice in size and type (including how long they've been using the software and, ideally, what version they're using currently)
VI. Product description
  a. How it performs the functions described in section IV
  b. Other functions it performs
  c. Product brochures, etc.
  d. Software versions and release dates
VII. Hardware and network requirements
VIII. Customer maintenance and support
IX. Vendor training
X. Implementation plan
XI. Interface history and capabilities
XII. Proposed costs and payment schedule
XIII. Warranties
XIV. Sample contract

physician-patient interaction [12]. Additionally, family physicians express disappointment that the systems neither save time nor generally improve care quality. To address these concerns, the American Medical Informatics Association (AMIA) has empaneled the EHR-2020 Task Force [13]. This Task Force embraced four core recommendations: (1) simplify and speed documentation, (2) refocus regulation to stress usability rather than evaluation and management

EHR DEMONSTRATION RATING FORM

Each person who observes vendor demonstrations should complete a form like the one below. The form you use should list the functionality that your selection group decided was most important to your practice. To analyze the results, assign 1 point to strongly disagree, 2 to disagree, 3 to unsure, 4 to agree, and 5 to strongly agree. Calculate average scores for each function and print a summary score sheet for each vendor.

PRODUCT: _____

DATE: _____

EVALUATOR: _____

Please evaluate the product based on all the information you have available at this time. If you need more information, please note that in your comments.

I. FUNCTIONALITY: This product performs the following functions with little user effort:

	Strongly disagree	Disagree	Unsure	Agree	Strongly agree
Results reporting (lab/X-ray)					
Progress/consult notes					
E/M coding					
Telephone message documentation and tasking					
Chart documentation (problem list, medication list, allergies, vital signs, health maintenance, trending lab values, etc.)					
Order entry (lab/X-ray)					
Prescription writer					
Formularies					
E-fax to outside physicians					
Remote access (e.g., to off-site transcription or physician's home)					
Referral management					
Charge capture without manual entry					
E-mail (encrypted)					
Health maintenance alerts					
Medical decision support tools					
Patient education materials					
Security (passwords, audit trails)					

Comments: _____

_____

_____

II. OVERALL EASE OF USE AND FLEXIBILITY

	Strongly disagree	Disagree	Unsure	Agree	Strongly agree
This product allows individual user-specific customization					
This product minimizes user data input					
This product offers multiple note creation options					

Comments: _____

_____

_____

Fig. 4 EHR demo rating form (From: Adler [4]. Request for reprint submitted)

(E&M) coding, (3) increase transparency among EHR vendors by publishing interface application programming interfaces (APIs, tools for linking to the computer programs within EHRs), and (4) foster innovation with the focus of EHRs as an open platform. The Task Force has drawn heavily on recommendations in the report, "A Robust Health Data Infrastructure," published by

VENDOR RATING TOOL

For each EHR product you are considering, assign a ranking from 1 to 5 (with 5 being best) for each of the criteria listed in the functionality and vendor characteristics categories below. Total the rankings for each vendor to determine a combined score for each category, then assign an overall ranking. For the cost section, supply a dollar amount for each criteria listed and then rank each vendor based on your assessment of its total initial and total annual costs. Next, consider the relative importance of the three categories and assign a percentage to each (e.g., functionality = 40 percent, cost = 20 percent and vendor characteristics = 40 percent). Finally, use these percentages to calculate the weighted scores for each vendor.

FUNCTIONALITY	VENDOR 1	VENDOR 2	VENDOR 3	VENDOR 4	VENDOR 5
Quality/presence of features we prioritized (see demo rating summaries)					
Ease of use (e.g., minimizes typing, is intuitive, simple layout)					
Speed (network/hardware configuration, minimizes keystrokes)					
Individual user flexibility • Multiple note creation options (transcribe, voice, template) • Provider can modify/create own templates • Provider can create own macros					
Preloaded templates and patient education					
Combined functionality score (total the rankings for each vendor)					
A Overall functionality ranking					

COST	VENDOR 1	VENDOR 2	VENDOR 3	VENDOR 4	VENDOR 5
Initial hardware and network upgrades					
Initial interfaces					
Initial software					
Total initial cost					
Annual software maintenance (includes upgrades and support)					
Annual interface upgrades					
Total annual cost (excludes initial costs)					
B Overall cost ranking					

VENDOR CHARACTERISTICS	VENDOR 1	VENDOR 2	VENDOR 3	VENDOR 4	VENDOR 5
Training					
Support					
Implementation					
Software upgrades					
Company stability					
Combined vendor characteristics score (total the rankings for each vendor)					
C Overall vendor characteristics ranking					

D Functionality	%
E Cost	%
F Vendor characteristics	%
	should total 100%

OVERALL RANKING	VENDOR 1	VENDOR 2	VENDOR 3	VENDOR 4	VENDOR 5
G Weighted functionality score ((A × D) ÷ 100)					
H Weighted cost score ((B × E) ÷ 100)					
I Weighted vendor characteristics score ((C × F) ÷ 100)					
Weighted overall score (G + H + I)					
Final Ranking					

Fig. 5 Vendor rating form (From: Adler [4]. Request for reprint submitted)

the JASON group of the MITRE Corporation for the Agency for Healthcare Research and Quality (AHRQ) [14]. This report promoted the concept that all EHRs should publish an open API that could facilitate interoperability, and that this "public" API should become a component of the requirements for EHR product certification [15]. This project remains in its early stages but EHR

Table 1 Summary of incentive payments available to eligible providers (EP) based on calendar year (CY)

Maximum incentive payments based on the first CY in which an EP demonstrates meaningful use				
	Maximum incentive payments based on the first CY in which an EP participates in the program			
Calendar year	2011	2012	2013	2014
2011	$18,000			
2012	$12,000	$18,000		
2013	$8,000	$12,000	$15,000	
2014	$4,000	$8,000	$12,000	$12,000
2015	$2,000	$4,000	$8,000	$8,000
2016		$2,000	$4,000	$4,000
Total	***$44,000***	***$44,000***	***$39,000***	***$24,000***

users should follow the group's progress in promoting usability and interoperability of electronic record products.

Clinical Decision Support (CDS) Tools

EHR technology potentially affords user access to a multiplicity of clinical decision aids: point-of-care access to reference material, evidence-based recommendations specific to the diagnosis, reminders, and algorithmic recommendations specific to the patient context all become possible [16]. However, challenges remain in accomplishing widespread adoption of these tools: existing systems have gained mixed acceptance due to interface issues and workflow disruption, patient summaries provide insufficient actionable data, and techniques for integrating multiple guidelines for competing comorbid health states remain elusive [17]. The most straightforward CDS tools consist of disease-specific order sets and templates that present when seeing a patient with a particular diagnosis. To create more complex tools that incorporate patient-specific characteristics and preferences, developers must turn to more sophisticated techniques. Rule-based systems rely on coded logic that uses patient-specific information to tailor recommendations. These systems use a number of different logic coding systems (Arden Syntax, GLIF, GELLO) to integrate guideline recommendations with patient information derived from the EHR database structures [18–20]. These coding environments are not generally accessible to practitioners but rather require working with trained informaticists for implementation.

Online reference services provide information at the point of care to support decision-making at the point of care [21]. A number of subscription services exist in the USA to provide such support: DynaMed® [22], UpToDate® [23], and Epocrates® [24] represent several popular examples. These applications provide reference support such as evidence-based summaries for clinical disorders, formulary information, and drug-drug interactions. The developers have provided apps for the Apple® and Android® smart devices to provide convenient real-time access in the context of patient encounters. These tools promise to improve concordance with clinical guideline recommendations and currency of clinicians' medical knowledge [25, 26].

Standards

Physicians have historically entered clinical data as unstructured free text in paper records. While the free-text approach provides for rich detail and nuance related to the doctor-patient interaction, the lack of standardized terminology limits users' ability to search such record entries for terms and concepts that can be compared across different record systems. A number of standard vocabularies and terminologies have come into use to facilitate extraction of common terms from different clinical systems. SNOMED-CT (Systematized Nomenclature for Medicine-Clinical Terminology) represents a hierarchical vocabulary system consisting of over 400,000 terms [27]. SNOMED-CT provides access to multiple synonyms for a single concept, providing

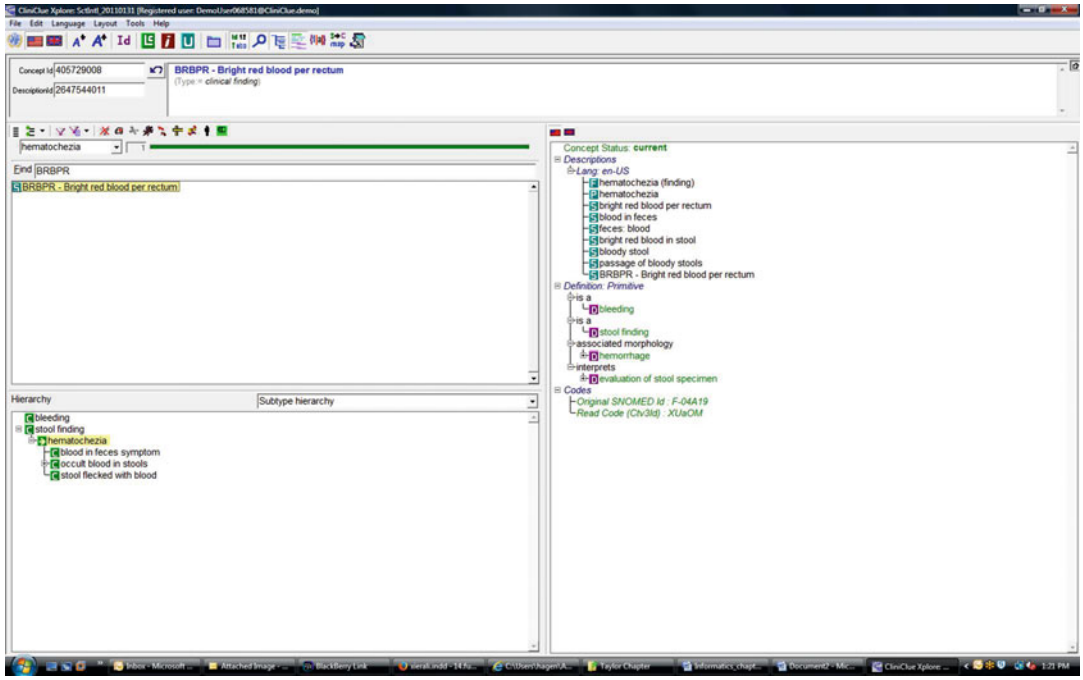


Fig. 6 Example of SNOMED-CT demonstrating the synonyms mapped to "hematochezia" in the terminology

means for mapping to a single standard term multiple different ways of expressing a notion. For example, "rectal bleeding" might appear as "hematochezia" in one user's records, while another user might express rectal bleeding as "bright red blood per rectum" or the abbreviation "BRBPR" (Fig. 6). While no particular terminology has been found to perform perfectly, SNOMED-CT appears to identify primary care terms better than several other options, although at a suboptimal rate [28, 29]. Medical Subject Headings (MeSH) represents a controlled vocabulary used by the National Library of Medicine for categorizing and coding entries in the MEDLINE® and PubMed® literature retrieval services. The Logical Observations, Identifiers, Names and Codes (LOINC®) system provides names and codes for laboratory examinations, vital signs, and radiology studies [30], while RxNORM provides support for mapping among various pharmaceutical terminologies [31]. Fortunately, the Unified Medical Language System (UMLS) represents an additional candidate for standard vocabulary access [32] that includes a number of tools for manipulating and mapping to multiple medical terminologies (most specifically the Metathesaurus, which provides a tool for identifying synonymous terms from systems such as SNOMED-CT®, ICD-10-CM, CPT®, and LOINC®.) These systems as well as other standards will facilitate the interoperability of electronic health records for sharing patient data among various health-care organizations [33].

Patient Portals

The meaningful use requirements discussed earlier include components of "patient engagement," to include patients' access to their clinical records, prescriptions, laboratory data, and messaging with their providers [34]. The various EHR vendors will obviously implement these features differently, but most will provide patients with access to commonly desired functions such as prescription refills, review of medical record

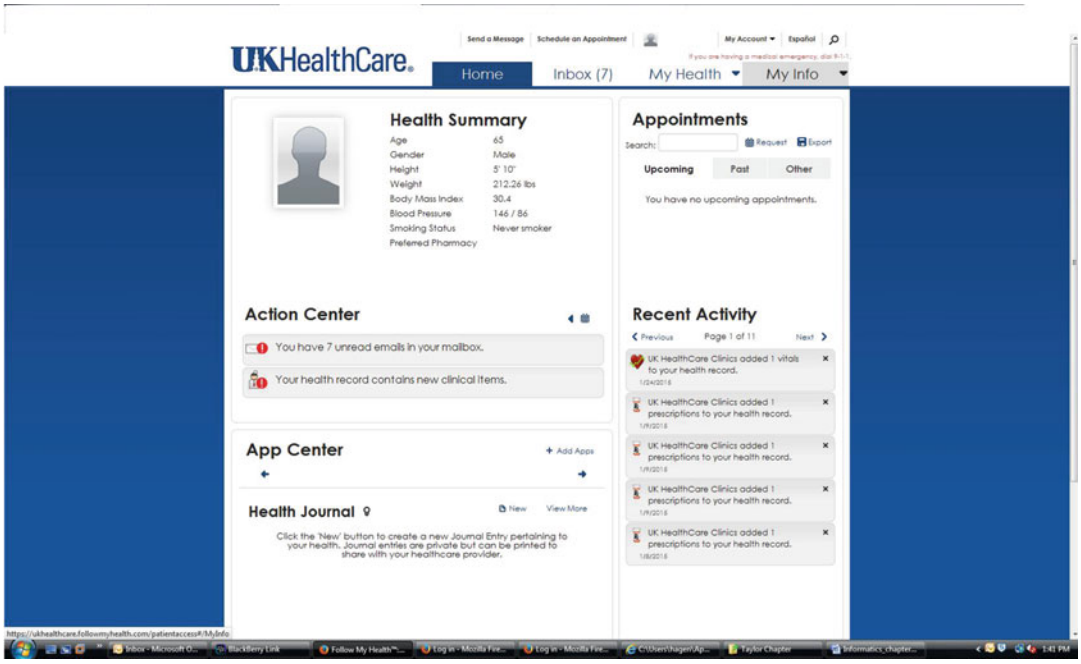


Fig. 7 Example of the "Follow My Health" patient portal provided for patients in the University of Kentucky Healthcare system

information, and secure messaging with their providers [35]. Figure 7 demonstrates one example of such a patient portal interface. Advent of these portals necessitates familiarity with the components of the Health Insurance Portability and Accountability Act (HIPAA), which outlined a number of requirements that providers must observe in managing and sharing patient information. In particular, HIPAA mandates strict requirements for providers' release of "protected health information" and the education of providers regarding these requirements. HIPAA also includes standards for electronic transmission of these data [36].

Telehealth

As broadband access to the Internet and the World Wide Web has expanded, so too has the potential for using health information technology for remote health-care service. Historically, this required dedicated expensive video and audio installations that most users and facilities could not afford. Faster computers and enhanced broadband speeds have made remote access to health services available using a personal computer or tablet device and an Internet connection. Applications include remote interpretation of radiology studies, consultations, and direct patient-physician interaction. These types of remote interactions have raised challenging issues regarding credentialing: is the physician who conducts a consultation with a patient residing in another state practicing in that state without a license? Licensing jurisdictions vary in how they regard these interactions. Most recently, the Federation of State Medical Boards has proposed a reciprocal licensing process that might support these activities [37].

Informatics and Population Health

The increasing pervasiveness of electronic health records affords access to potentially enormous quantities of data for research and identifying patterns of disease. Interoperability among these records can afford efficiencies and eliminate duplication in ways not possible with historical

paper record systems; indeed, one group has estimated that integrated information technology systems could save as much as $78 billion annually in health-care expenditures [38]. Additionally, geographic information systems (GIS) can utilize such data to identify patterns of utilization and patient care access to guide organization of health-care services [39]. Aggregation of data in registries can also identify potential population quality issues that might not appear readily in a single practitioner's experiences [40].

The Learning Health System

Interoperability of health information systems and vast amounts of patient care data provide the opportunity to learn in real time from our daily care activities. The Institute of Medicine (IOM) in 2012 issued its report, "Best Care at Lower Cost. The Path to Continuously Learning Health Care in America," in which the authors identified ten recommendations for enhancing application of the best evidence at the point of care: (1) improve the capacity to capture clinical, care delivery process, and financial data for better care, system improvement, and the generation of new knowledge; (2) streamline and revise research regulations to improve care, promote the capture of clinical data, and generate knowledge; (3) accelerate integration of the best clinical knowledge into care decisions; (4) involve patients and families in decisions regarding health and health care, tailored to their preferences; (5) promote community-clinical partnerships and services aimed at managing and improving health at the community level; (6) improve coordination and communication within and across organizations; (7) continuously improve health-care operations to reduce waste, streamline care delivery, and focus on activities that improve patient health; (8) structure payment to reward continuous learning and improvement in the provision of best care at lower cost; (9) increase transparency on health-care system performance; and (10) expand commitment to the goals of a continuously learning health system [41]. The Learning Health System Initiative has embarked on making these recommendations reality [42, 43].

Clinical Informatics as a Specialty Option

As information systems have become more prevalent and integral to daily practice, the need for trained informaticians has arisen and grown. In 2009, the American Medical Informatics Association developed and published proposed standards for training and certification in a new specialty of clinical informatics [44–46]. The American Board of Medical Specialties (ABMS) approved the new clinical informatics subspecialty in 2011, and two sponsoring boards (the American Board of Preventive Medicine, ABPM, and the American Board of Pathology, ABPath) agreed to serve as sponsoring boards for the new subspecialty certificate. Family physicians can qualify through the ABPM, while pathologists must apply through the ABPath. Two routes exist to qualify to sit for the certification examination: completion of an ABPM-approved fellowship program or documentation of substantial experience in informatics practice. The latter practice experience route will exist for 5 years only, after which completion of an approved fellowship training program will represent the only route to clinical informatics certification. The Accreditation Council for Graduate Medical Education has developed standards and processes for accrediting new and existing informatics training programs [47]. ABPM administered the first examination in 2013, and approximately 80 family physicians succeeded in becoming certified clinical informatics subspecialists [48].

Information technology has revolutionized family physicians' access to tools to both organize their patients' clinical information and support the critical patient care decisions they make day to day. The available systems are at once complex and powerful, but not always user-friendly. The new specialty of clinical informatics provides a route for those who wish to gain additional expertise in both the technical operation and management of these systems. For those who do not want to make such a

formal commitment, good general coverage informatics textbooks [49, 50] can provide more in-depth coverage of this rapidly expanding component of modern family medicine practice.

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Occupational Health Care

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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. These considerations have led to a revised approach to work injuries. Occupational medicine is now focused on maintaining functional capacity by returning injured workers to productive employment via appropriate work restrictions 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 healing entity, coupled with the development of novel compounds and industries, such as graphene and nanotechnology, presents ongoing health challenges for workers and occupational medicine providers.

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 preventative medicine, OEM is one of the smallest medical specialties recognized by the American Board of Medical Specialties. However, the expertise OEM provides in regard to worker health and population management skills renders it an ever important specialty.

Despite this need, there is a shortage of OEM physicians. Indeed, only 83 physicians achieved board certification in OEM [3]. In addition, with

the number of board-certified occupational medicine specialist 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 [4]. 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 2013, there were approximately three million nonfatal workplace injuries and illnesses reported in private industries. More than half of these involved an injury severe enough to require work modifications, job transfer, or time off from work [5]. Private sector laborers, freight/stock/material movers, and heavy/tractor trailer truck drivers reported the greatest number of days off work due to a workplace injury or illness. Persons 45–54 years of age had the highest incidence of injuries, suffering a rate of 119.9 per 10,000 workers. Males had an incidence rate of 119.2 per 10,000, substantially higher than the female rate of 97.0. Some of the most common causes of work injuries across all industries were musculoskeletal disorders (36 %), contact with objects (25 %), same-level falls (17 %), and overexertion (12 %) [6].

While rarely considered during national debates over the financing of medicine, the direct cost associated with work-related health care is tremendous. In 2012, the cost of worker's compensation-related health care was approximately 62 billion dollars, split nearly evenly between medical and indemnity costs [7]. This cost closely approaches the estimated total 2012 US cost associated with the treatment of asthma (75.9 billion), mental disorders (83.6), and cancer (87.5 billion) [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. While this data increasingly provides 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 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. Before workers' compensation, 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 or not 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 their local jurisdiction nuances [1].

Occupational Health and Safety Administration

At the turn of the twentieth century, workplace industrial accidents became more publicized and public outrage increased. In the wake of disastrous workplace accidents, such as the Triangle Shirtwaist Factory fire, regulatory agencies and acts, such as the Safety Appliance Act and the United States Bureau of Mines, took form. With the increased 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 chemical, many of which had unknown health effects. It is estimated that in 1970, there were 14,000 work-related fatalities in the USA.

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 USA 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 agency's many services include regulatory inspections and enforcement of standards, such as those pertaining to lead and blood-borne pathogens [9].

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 perform research on worker injury/illness and to make recommendations on workplace safety issues. Examples of NIOSH's research areas include the danger of antineoplastic medications to health-care workers and offshore gas/oil extraction. In addition, NIOSH also funds education, research, and training in occupational health through 18 education centers, 10 agriculture disease-related centers, and 28 training grants. The roles of NIOSH and OSHA are distinct, with OSHA being the regulatory aspect of work safety [10].

Americans with Disabilities Act (ADA)

The purpose of the ADA, first passed into law 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 [11]. The ADA was one of the most important pieces of social legislation in the USA and represented a major change in thinking. A particular 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 as long as 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 taking into account 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.

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 1,250 h 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 [12].

Many family physicians encounter this piece of legislation as a multipage form with a request 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

Understandably, 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 [13]. 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 future 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 [14].

Medications and Substances

Outside of the obvious dangers of alcohol and illicit drug use at work, several medications can result in sedation and other dangerous side effects. There has been a massive increase in opioid use in health care [15]. Likewise, there is growing potential for prescription medications, such as opioids, to 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. 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 nonwork-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 the examination. Indications of nonorganic etiologies should also be noted.

The Occupational History

Understanding the nature of a patient's work is vital for the treatment and management of work-related medical conditions. Many US physicians currently rarely inquire about work activities during clinical encounters [16]. 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 [17]. 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 not sufficient 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.

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 [18]. Based on such findings, ACOEM guidelines recommend assessing for psychosocial factors, such as work monotony, relationship with supervisors, and job satisfaction [14]. 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 [19].

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 [20]. Unchecked catastrophizing by the worker has been shown to impede improvement [21]. Thus, thorough and clear communication 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 [22]. 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 duty 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. This in turn is associated with risks of repeated or new injuries associated with loss of vigilance during work tasks. 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 [23]. 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 [24].

Return to Work

It is now apparent that 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 family 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 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 [25]. 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 [26]. One of the unifying features of the guidelines is the use of a step-based algorithm [27].

The proper use of the algorithms is dependent on having a sound understanding of the definitions of restrictions, limitations, and tolerance [28]. 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 [27].

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 as a whole. The family physician should try to gain an understanding of the job tasks and direct the worker/patient accordingly.

Representative Common Occupational Conditions

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 [29]. In 2013, musculoskeletal disorders accounted for 33 % of nonfatal workplace injuries in all industries. Sprains, strains, and tears were most common, accounting for 38 % of all injuries requiring time off work. The most work-affected body parts were the back (36 %), shoulder (12 %), and knee (12 %). Injuries were most frequent among nursing assistants, laborers, and freight/stock/material movers [4].

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 [30–32]	Repetitive loading of spine Inadequate rest time at work Awkward lifting Prolonged standing High job demand/stress	Psychiatric disorders Age Smoking
Carpal tunnel syndrome [32–34]	High hand force Prolonged hand force Vibration Repetitive motion	Diabetes Pregnancy Hypothyroidism Genetic predisposition
Rotator cuff tear [32, 35]	Prolonged shoulder flexion Forceful pinching Work above at or above shoulder height Work stress	Age Overhead sports
Slips and falls [36]	Weather Poor lighting Slippery surfaces	Inappropriate footwear Age Fatigue

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: Infections

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 frequently, 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. 82 % involved percutaneous injuries and 79 % percent involved blood products. Nurses and providers were the most frequently injured, involved in 72 % of cases [37].

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). In an effort 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 postexposure 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. For example, the incidence of pertussis, measles, and even Ebola has increased in recent years, and the management of work-related outbreaks of these infections can become the responsibility of the family during the care of a community. In addition, classic concerns such as tuberculosis, chicken pox, conjunctivitis, streptococcal pharyngitis, malaria, and typhoid fever can wreak havoc on the worker and workplace. The management of each of these conditions is outside the scope of this chapter, and the reader is directed to the CDC for further direction.

Finally, zoonotic infections can also pose serious risks for 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 7,500 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 industrial chemicals. Table 3 summarizes some of the most well-known chemically and environmentally induced health conditions.

The chemical and environmental exposures most likely encountered by the family physician are limited to a few select 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). 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 [43].

Symptoms from the reaction 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 [32].

Sick Building Syndrome

Sick building syndrome (SBS) refers to a constellation of general symptoms attributed to indoor

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 four vaccines 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 tropic 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 [32, 38, 39]

environments [44] including 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

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 several 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 700–1,000 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 [41, 42]

the irritation threshold concentration can cause symptoms, especially those with low odor thresholds.

Several factors can contribute to indoor air quality detriments. Environmental elements to consider when assessing SBS include building ventilation rates, temperature and temperature fluctuations, humidity, chemicals (i.e., formaldehyde and ozone), and odors. Personal factors, such as atopy and contact lens use, and psychosocial factors have linked to SBS.

As SBS can involve significant anxiety, clear and open communication is important to effective management. Initial evaluation begins with an interview of affected 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 [45]. Similar to SBS, 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 symptom and consists primarily of removing the source of moisture and visible mold contamination [46]. 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 preventative 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.

Posthire, Preplacement Examinations

ADA prevents employers from discriminating against applicants on the basis of 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 posthire, 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 examinations are sometimes necessary when an employee has been off of work for an extended period of time. Similar to 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 results are not to the workers' desire. In such confusing scenarios, rather than contributing unnecessary risk to the patient, other workers, or the public, we suggest that family physicians seek the assistance of their occupational medicine colleagues.

Commercial Driver Medical Examinations

In 2013, there were 4,405 fatal occupational injuries [47]. Two out of five of these fatalities were transportation-related events. Of the 1,740 transportation-related fatalities, three out of five involved motorized land vehicles. With such data, ensuring the safety of commercial drivers and public roads is one of the most important concerns of occupational medicine and also one of the most common avenues for family physicians to provide occupational health care.

To obtain a commercial driver 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, all commercial driver examinations be performed by certified commercial driver examiners [48]. Certified commercial driver medical examiners receive standardized training and must pass a certification examination. This move has reduced the number of available examiners and provides family physicians a both important and lucrative occupational health opportunity.

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 a defined population. With additional training, the family physician can assist with such programs.

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Problems Related to Physical Agents

Christopher S. McGuire and J. Brian Lanier

Contents

Heat

Environmental heat injury to humans involves a spectrum of disorders. Ranging from mild to severe, these include heat cramps, heat syncope, heat exhaustion, and exertional heat stroke.

Nonathletic heat injuries occur most often in the elderly, especially those in summer heat waves who live without air conditioning. For example, an August 2003 heat wave in Europe resulted in 14,800 deaths (**Arguard**). During this time period one hospital in France experienced 83 admissions, with a 65 % death rate (**Arguard**). Use of antihypertensives and residing in an institution were associated with worse outcomes. Most survivors had a reduced functional status and were not able to be discharged to independent living.

Athletes are another group of individuals who are susceptible to heat injuries. It is estimated that more than 9,000 high school athletes are treated for exertional heat injuries each year, most occurring during the start of the academic year (Kerr2). High school football players are especially vulnerable, as they have the highest rate and absolute numbers of heat injuries (kerr2). Between 1995 and 2010, 35 football players died from heat injuries (Kerr2). Exertional heat injuries can be prevented through a gradual acclimatization to the heat. The National Athletic Trainers Association publishes guidelines for a heat acclimatization process (Casa). Hallmarks include limiting practice times, early practices with helmet only,

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and mandatory breaks between practice sessions in a cool environment.

Sudden cardiac death in athletes participating in endurance sports has been a concern. However, a recent analysis of runners demonstrated that serious heat injuries were ten times more common than cardiac arrhythmias (Yankelson). Additionally, hyponatremia must be in the differential diagnosis for a collapsed athlete. In a 9 h endurance event, it only takes approximately 2.2 l of excess fluid for a 50 kg female to decrease her plasma sodium concentration to 120 mEq/L (Armstrong). An on-site sodium concentration analyzer can be helpful in the evaluation of a collapsed athlete with a near-normal temperature (Wen).

There is no established method for evaluating a return to sports for an athlete that has suffered a heat injury. The Israeli Defence Force has developed a protocol where a soldier walks on a treadmill in a hot (40 °C), humid (40 % RH) room with continuous rectal temperature monitoring (Johnson). A case report of an endurance athlete who had two serious heat-related incidents demonstrated that cycling in a heated room with continuous gastrointestinal temperate and heart rate monitoring could improve heat tolerance. He was then allowed to return to racing and completed several more races in extreme heat stress without incident. Both of these methods are probably not practical for most primary care providers.

Most studies report submersion in ice water as the most effective treatment (Lipman). Natural sources of water can be used, such as rivers, lakes, or the ocean. Care should be taken that the head is kept above the water and that the patient is never left alone. However this is not always practical, and the next best option is removing any clothing or equipment (football helmet, bullet-proof vest, etc.), dousing the patient with cold water, and creating a wind source to facilitate convective cooling, such as a fan. Moving the person to shade also helps but mostly when temperatures are less than 20 °C (68 °F).

The following table is taken from the Wilderness Medical Society Practice guidelines (Lipman):

Severity of Heat-Related Illness	Diagnosis	Treatment
Mild	Heat cramps	Oral isotonic or hypertonic fluid replacement
	Heat edema	Extremity elevation Compression stockings
Moderate	Heat syncope	Removal from heat source Passive cooling Oral isotonic or hypertonic fluid hydration
	Heat exhaustion	Removal from heat source Evaporative and convective cooling Oral or intravenous isotonic or hypertonic fluid hydration
Severe	Heat stroke	Remove from heat source Supportive care of airway, breathing, circulation Cold-water immersion Evaporative and convective cooling Intravenous hydration Evacuation

Cold

Approximately 700 people a year die in the USA from hypothermia (Petrone). Men between the ages of 30 and 49 years are the most commonly affected. Medical conditions such as malnutrition, hypoglycemia, and dementia can predispose individuals to cold injuries. However, the single most common cause is alcohol intoxication.

Mild hypothermia is defined as a core body temperature of greater than 32 °C. The initial management can be accomplished by passive rewarming. This includes removing wet clothing, applying insulating clothing, and moving into a protected area with warm, moist air (Petrone).

The next step is active rewarming. This can be accomplished by submersion in warm water or a forced air rewarming system, such as a Bear Hugger (3 M™ Bair Hugger™ therapy, St. Paul,

Minnesota, USA). The last step is active internal warming. This involves body cavity lavage techniques or extracorporeal rewarming. Infusing warm saline is not an effective technique, as the relative heat transfer from a 1–2 kg amount of warm fluid into a 60–80 kg cold person is small.

Frostbite

Frostbite and nonfreezing cold injuries (NFCI) were once mainly a military health problem; however, with increasing interest in outdoor activities, the incidence in the general population is increasing (Imray). The mainstay of treatment is rapid rewarming. As with hypothermia, the main predisposing factor is alcohol consumption.

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, with occasional upper extremity involvement. There is rarely any tissue destruction; however, the sequela can be as severe as frostbite. The hallmark of NFCI is a sensory neuropathy that can result in severe pain, edema, and hyperhidrosis. Some individuals are unable to continue to work outside in cold temperatures, which can affect their occupational career as well as recreational opportunities. Prevention remains the key, with encouragement to change into dry socks and/or gloves as well as airing feet several times a day.

The chance of frostbite and NFCI is more correlated with duration of exposure rather than absolute temperature (**Valnicek**). Most often the hands and feet are affected (90 %), but the face, perineum (from sitting on metal seats), and penis (underdressing while running) can be affected.

The pathophysiology of cold injury consists of four phases, the "prefreeze phase," "freeze-thaw phase," "vascular stasis phase," and "progressive or late ischemic phrase." Skin sensation is lost around 10 °C. This induces vasoconstriction. The vascular supply vasodilates in approximately 5–10 min cycles in an attempt to save the extremities. If the temperature falls below 0 °C, eventually ice crystals will form in the extracellular fluid and progress to endothelial damage. The final phase involves thrombosis, ischemia, necrosis, and gangrene.

The extent of tissue damage after injury is difficult to predict based on initial presentation or exam. However, favorable signs include intact sensation, normal skin color, and clear fluid in blisters (Imray). Traditionally, a 3–6 week wait was necessary to determine the full extent of damage prior to surgery. Triple-phase bone scanning may allow an early diagnosis of viability and assist the physician and patient with prognosis.

Prehospital care of frostbite and NFCI involves warming the core by moving out of the wind into shelter and drinking warm fluids. The next step is removing any wet clothing and placing the affected areas in a dry, warm area, such as a companion's axilla. Do not rub the extremity. Aspirin (81 mg) and ibuprofen (800 mg) may help through antiplatelet and antiprostaglandin effects. Tissue that is rewarmed and refrozen almost always becomes necrotic, therefore the decision to rewarm by submersion in warm liquids must include an evacuation plan. The patient should not walk on rewarmed feet (Imray).

The initial hospital management consists of correction of hypothermia, rewarming in a 37–40 °C whirlpool, antibiotics, antitetanus prophylaxis, and ibuprofen. Vasodilators (iloprost, pentoxifylline, and buflomedil) and tPA have been used with some success.

Radiation

Medical imaging is a significant source of man-made radiation [21]. Most of that radiation is due to computed tomography (CT) scans. Plain radiographs use doses of radiation that are approximately 100 times lower. The use of CT has increased dramatically since its introduction in the 1970s (Brenner). This is especially true for children, who represent about 11 % of CT scans (Brenner). There is good evidence from atomic bomb survivors as well as radiation workers that a dose of radiation equivalent to two to three CT scans results in an increased risk of cancer. The evidence is very convincing for children (Brenner).

Many physicians underestimate the risks of radiation from CT. A study noted that 53 % of radiologists and 91 % of emergency room physicians did not believe CT increased the lifetime risk of cancer (Lee). The cancers most correlated to radiation exposure are lung and leukemia (Brenner Radiology 232:735).

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 recommends no imaging for an uncomplicated headache and no imaging for a suspected pulmonary embolism without a high pretest probability (including a positive d-dimer). Additionally, ultrasound should be the first choice for imaging evaluation of children with appendicitis (choosing wisely.org)

Exposure to radon gas is the second leading cause of lung cancer, behind smoking (BMJ 330:223). There are approximately 21,000 lung cancer deaths each year in the USA attributed to radon (Lantz). Radon is a radioactive, colorless, odorless gas that is naturally released from the ground and can build to toxic concentrations inside many homes. Basements are particularly vulnerable. The average radon level outdoors is 0.4 picoCuries per liter of air (pCi/L) and 1.3 pCI/L inside houses in the USA. The US Environmental Protection Agency limit is 4.0 pCi/L. At that level it is estimated that the lifetime risk of radon-induced lung cancer for never smokers is 7 per 1,000 exposed and 62 per 1,000 exposed smokers. Many public health authorities recommend screening homes with readily available screening kits. Remediation is effective and relatively inexpensive.

Ultraviolet light

Ultraviolet light (UVL) exposure is linked to melanoma and nonmelanoma (squamous and basal cell) skin cancers (IARC working group). These are the most prevalent cancers in the USA. This UVL exposure can occur in the form of excessive natural sun exposure as well as indoor tanning. The risk of cutaneous melanoma is increased by 75 % with artificial tanning use before the age of 30 (IARC2).

However, multiple studies have shown an inverse correlation between sun exposure and overall cancer rates (Bendik, Grober, Grant1, Grant2, Grant3). This is possibly due to a link between Vitamin D deficiency and cancer. Approximately 90 % of vitamin D is produced from skin exposure to sunlight. The benefits of sun exposure in reasonable doses may outweigh the risks.

Electrical Injury

In the USA there are approximately 50 fatal nonoccupational electrocutions per year (CPSC data) and approximately 50 lightning deaths per year (national weather service). However, there are many nonfatal injuries that can result in significant morbidity (Wesner). In general, electrical injury produces more injury to bone, nerve, or muscle than thermal injury does.

Electrical injuries cause the immediate effects of thermal burns, cardiac arrhythmias, seizures, as well as nerve deficits. The initial management includes removing the person from the source of injury (without electrocuting the rescuers) and providing basic life support. Long-term sequelae include neurological injury at the site of entry of the current resulting in chronic pain or other neuropathic sensations. The mechanism of action of injury is not completely known. Central nervous system injuries have also been reported, with a presentation similar to traumatic brain injury. Patients present with difficulty with verbal memory, attention, as well as behavioral changes. This can be present after even minor electrical injuries (Wesner).

Noise

Exposure to excessive sound pressure levels (noise) is the leading cause of preventable hearing loss (Basner). Nonoccupational sound sources include social (amplified music, recreational firearm use, etc.) as well as environmental (living

near airports, subways, etc.). The mechanism of hearing loss is destruction of auditory sensory cells in the cochlea. There is no known cure.

Long-term effects include hearing loss that can interfere with speech understanding as well as tinnitus. Tinnitus usually occurs with an acute or chronic noise exposure. Their association is likely due to similar pathophysiological pathways.

Many youth are exposed to loud noise, mostly due to amplified music. One survey reported over 50 % (mean age 19 years) experiencing temporary tinnitus as the result of noise exposure at a concert or club (Katbamna). Personal headphone use has also dramatically increased. The reported prevalence of listening to music through headphones has increased from 19.8 % in 1988–1994 to 34.8 % in 2005–2006 (Henderson). However, other studies have reported no increased rates of noise-induced hearing loss in 12–19-year-olds from the 1988–1992 to 2005–2006 time periods (Henderson).

There are also nonauditory health effects from noise exposure (Basner). The major effect is on sleep quality. Even levels as low as 33 dB have been shown to activate the autonomic system. Additionally, long-term exposure to noise is implicated in hypertension, ischemic heart disease, and stroke (Basner)

Carbon Monoxide

Carbon monoxide (CO) is a poisonous, odorless, tasteless gas. The most common exposure in the community is due to inefficiently burning hydrocarbons. Examples are internal combustion engines and home heating systems. CO molecules readily combine with hemoglobin to form carboxyhemoglobin and reduce the oxygen-carrying capacity of blood. Additionally, CO directly poisons mitochondria and is implicated in oxidative stress of cells (Guzman)

There are approximately 430 non-fire-related carbon monoxide deaths per year. Additionally it is estimated there are 25,000 hospitalizations due to CO exposure. Treatment with 100 % oxygen is indicated.

Blood carboxyhemoglobin levels can be directly measured through most blood gas analysis machines. Baseline levels in smokers are higher than nonsmokers. Sometimes carboxyhemoglobin levels do not correlate with exposure. Most pulse oximeters cannot reliably distinguish between carboxy and oxyhemoglobin and will be falsely elevated in CO poisoning (Guzman).

The initial treatment for CO poisoning is 100 % oxygen via nonrebreather mask as well as supportive care. The patient may have cardiac ischemia as well as arrhythmias. Severe poisoning can result in metabolic derangements. Treatment with hyperbaric oxygen (via a dive chamber) is controversial but may benefit severely intoxicated patients. CO poisoning in pregnancy is a unique problem, as it is difficult to assess oxygenation status of the fetus and fetal hemoglobin has a higher affinity for carbon monoxide than adult. Pregnant women may uniquely benefit from hyperbaric oxygen.

CO poisoning is easily prevented by correctly installing furnace venting, and running internal combustion engines in well-ventilated areas. Inexpensive home carbon monoxide alarms are available.

Most CO poisoning victims recover without sequela. There is some description of a delayed-onset neurological sequela. This can involve long-term neurocognitive effects as well as depression and anxiety. Many of these symptoms can last 12 months or longer (Guzman).

Pediatric carbon monoxide exposure can have different effects than on adults. Often children do not report any headache and present with seizures or perturbations in consciousness (Cho). Children have a lower rate of delayed neurological sequelae than adults, 2–10 % versus 10–40 % (Cho). Additionally, there are few guidelines for the use of hyperbaric oxygen in children.

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Bites and Stings

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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 chapter "▶ 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 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 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 rabies vaccine adsorbed (RVA), the first dose given simultaneously with HRIg with repeat doses on days 3, 7, 14, and 28. 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 (*Lactrodectus 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].

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.

Table 1 Antivenins

Antivenin	Indication	Dosage
Antivenin (Crotalidae) (BTG International) Polyvalent	Pit viper envenomation	See text
Antivenin *(Micrurus fulvius)* (Wyeth Laboratories)	Coral snake envenomation	Asymptomatic: 3–5 vials Symptomatic: 6–10 or more vials
Antivenin *(Latrodectus mactans)* (Merck)	Black widow spider envenomation	1–2 vials 1M (IV in severe cases)
Scorpion antivenin (available through Arizona State University[a])	Bark scorpion envenomation	1–2 vials IV

[a]Not FDA-approved. Available to Arizona physicians only

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 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 [17, 18]. For minimal envenomations, up to 10 vials of antivenin are used and for moderate envenomation 10–20 vials [10]. The antivenin for crotalids (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 [19]. 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 %. 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.

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 chapter "▶ 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.

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.

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.

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 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 have thousands of stinging organs called nematocysts on their tentacles. Contact with these organs triggers the sting, which penetrates the skin and releases toxin.

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 [13]. Any adherent tentacles are removed with gloved hands, and the affected areas may be 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 and other marine animals must be avoided, even when apparently lifeless.

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Poisoning

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More than 2.2 million poison exposures were reported to United States poison centers in 2012 [1]a at least 88 % of which were by intentional or accidental ingestion. This chapter provides primary care clinicians with sufficient information to diagnose and comprehensively manage common oral poisonings associated with significant morbidity and mortality. Ingestions of acetaminophen, cyclic antidepressants, aspirin/salicylates, and benzodiazepines are discussed.

General Treatment Measures

When presented with a patient who has ingested toxic amounts of a substance, gastric decontamination should be considered if the ingested substance is highly toxic or if the amounts ingested are sufficient to cause harm to the patient. Activated charcoal is the most effective method of gastrointestinal decontamination and is used with or without gastric emptying. When indicated, gastric emptying by lavage is generally preferable to ipecac-induced emesis. However, gastric emptying should not be routinely used in all cases of toxic ingestion. The doses of these treatments are described in Table 1, with additional information provided in the following discussion.

Activated Charcoal

Indications

Administration of activated charcoal is the most effective method used to prevent absorption of ingested drugs and chemicals from the gastrointestinal (GI) tract. It is not effective for treating ingestions of corrosive agents, cyanide, iron, ethanol, ethylene glycol, methanol, lead, lithium, or organic solvents. Multiple dosing has been shown to be effective for ingestions of theophylline, phenobarbital, carbamazepine, dapsone, and quinine. It is possibly effective for ingestions of salicylates, tricyclic antidepressants, digoxin, digitoxin, piroxicam, phenytoin, dextropropoxyphene, disopyramide, nadolol, phenylbutazone, and sotalol [2]. Dosing information is outlined in Table 1. If a patient is to receive ipecac, activated charcoal should be withheld until ipecac-induced vomiting has stopped (usually 1–2 h after the last ipecac dose). Activated charcoal should never be given before ipecac therapy. Absolute contraindications to the use of activated charcoal include patients with an unprotected airway, intestinal obstruction, or a dysfunctional gastrointestinal tract.

Dosing and Administration

The initial dose of activated charcoal is usually about 5–10 times the amount of ingested substance or 1–2 g/kg (Table 1). This protocol results in adult doses of 50–100 g of activated charcoal and pediatric doses of 10–25 g. Multiple-dose therapy is usually administered until the patient passes a charcoal stool. A level measuring tablespoon contains about 5–6 g of activated charcoal. Activated charcoal is commercially available as a powder to be mixed with water or a ready-made suspension with or without the cathartic sorbitol. Although cathartics were once recommended, they are no longer considered the standard of practice; they may be used with multiple dosing if the patient has not produced a stool after two to three doses of charcoal. The powder form is mixed with tap water to form a slurry (which contains 15–120 g of ingredient depending on the strength); the slurry must be shaken vigorously, as charcoal does not mix well in water. This process can be avoided by using a ready-made suspension containing 25–50 g in 120–240-mL containers. The poor taste of the slurry or suspension can be improved by using the cherry-flavored products or by adding small amounts of fruit juice or chocolate; milk products should be avoided because they decrease the adsorptive properties of the activated charcoal.

Cathartics

Cathartics can be used in combination with activated charcoal to decrease GI transit time and further decrease toxin absorption. Sorbitol and

Table 1 Dosing and administration of ipecac and charcoal

Treatment	Age (years)	Dose (mL)	Frequency	Comments
Ipecac	0.5–1 1–12 >12	5–10 15 30	Repeat in 20–30 min if first dose is unsuccessful [give with 0.5 glass (<1 year) to 1 glass (>1 year) of water]	Do not give >2 h after ingestion; *do* not give after charcoal; do not use *ipecac fluid extract*
Activated charcoal (Liqui-Char, charco aid, actidose)	All	1–2 g/kg (initial dose)	Single dose (most substances); repeat (1 g/kg q4h) until charcoal stool: for theophylline, phenobarbital, carbamazepine, dapsone, and quinine	If ipecac is used, should wait until ipecac-induced emesis stops (usually 1–2 h after last dose of ipecac); use cathartic with first dose

magnesium citrate (or sulfate) are considered the cathartics of choice; irritant cathartics such as cascara, senna, phenolphthalein, and bisacodyl are not recommended. Sorbitol (adults and children receive 4 mL/kg of a 35 % solution) is the treatment of choice because it works faster than the magnesium salts. Magnesium citrate (adult dose 200 mL, children's dose 5 mL/kg) is an alternative. Cathartics may be administered after the first dose of activated charcoal but should not be repeated when multiple doses of activated charcoal are used.

Gastric Lavage

Indications

Gastric lavage is the preferred method for gastric emptying in patients with potentially life-threatening ingestions treated in emergency room settings [3]. Lavage is most effective if performed within 1 h of the toxic ingestion.

Contraindications

Patients who have ingested acidic or alkaline substances are not considered candidates for gastric lavage. Lavage should not be used in patients who have ingested low-viscosity hydrocarbons (kerosene, gasoline, paint thinner), strychnine, or acids or alkalis because of the potential of aspiration. However, lavage is indicated for ingested aromatic or halogenated hydrocarbons and hydrocarbons containing pesticides, camphor, or heavy metals. Risk of hemorrhage or gastrointestinal perforation should also be considered prior to lavage. The passing of a lavage tube may induce vomiting or retching, which may result in aspiration of the hydrocarbon substance. Aspiration can be prevented by endotracheal intubation with a cuffed tube to protect the trachea prior to gastric lavage.

Administration

Conscious patients should drink a glass of water before the gastric tube is passed. Remove all foreign materials (e.g., dentures) from the patient's mouth prior to inserting the gastric tube. A large-diameter orogastric hose [36–40 French (F)] is used for adults and 1 of 24–28 F in children. After confirming tube placement, remove the stomach contents using an irrigating syringe. When the stomach contents have been removed and sent to the laboratory for toxicologic examination, begin lavage by administering 100–300-mL aliquots of fluid (warm water or 0.45 % saline) until the lavage return is continuously clear for at least 2 L or a total of 10–20 L has been administered. At the conclusion of the lavage, activated charcoal 1 mg/kg is administered (followed by a cathartic, if used).

Ipecac

Indications

Ipecac syrup has traditionally been used for acute oral drug overdose and oral poisonings managed at home [4]. If possible, individuals attempting to manage an acute poisoning at home should contact a regional poison control center or an emergency facility prior to the administration of ipecac. The potential for serious toxicity and inability to be seen at a health care facility within 1 h of ingestion may be justifications for its use. However, the mean recovery of ingested substances is 28 % (range 25–50 %) if given within 1 h of ingestion, and ipecac appears to add no benefit compared to activated charcoal alone in terms of clinical deterioration and hospital admission. Furthermore, the American Academy of Pediatrics has recommended against the use of ipecac in the home setting [4]. If ipecac is used, it is most effective if emesis is induced within 1 h after a toxic ingestion; emesis after 1 h may recover less than 20 % of the ingested substance. Emesis usually occurs within 30 min, with the emetic effects lasting for up to 2 h. If the first dose is not successful, administer a second dose within 30 min of the first dose (maximum is two doses). If the second dose is not successful, begin administration of activated charcoal if it is applicable to the ingested substance (see Table 1 for dosing and frequency). Once the patient vomits, save the emesis contents for analysis. If emesis occurs and a decision is made to administer activated charcoal, the charcoal must be given after the cessation of vomiting.

Contraindications

Ipecac should not be used in patients who have ingested acids or alkalis because of the potential of aspiration. The use of ipecac in patients ingesting hydrocarbons is usually not recommended (same exceptions as with gastric lavage). Ipecac syrup should not be confused with ipecac fluid extract, which is 14 times more potent than ipecac syrup. Ipecac should not be used in patients with an impaired sensorium or seizures, those who lack a gag reflex, infants younger than 6 months of age, when gagging where vagal stimulation may cause bradycardia (patients taking calcium channel blockers, beta-blockers, clonidine, digitalis), those with coagulation defects, or following ingestion of substances that cause rapid changes in sensorium.

Adverse Effects

When ipecac syrup is used in the recommended doses, patients experience common adverse effects such as vomiting, diarrhea, and drowsiness. Other complications such as Mallory–Weiss tears, aspiration, and bradycardia have occurred.

Acetaminophen

Acetaminophen overdoses account for large numbers of patients seen in emergency rooms and primary care physician offices. Data from the 1999 Annual Report of the American Association of Poison Control Centers (AAPCC) Toxic Exposure Surveillance System (TESS) documented more than 104,400 ingestions of acetaminophen-containing medications that necessitated poison control center contacts in 1999 [1]. Children under the age of 6 years accounted for 38 % of these exposures; about 39 % of the poisoned were age 20 years or older. There were 177 deaths for all ages among those who took acetaminophen and combination products.

Pharmacokinetics

Acetaminophen (APAP) is rapidly and completely absorbed from the GI tract following ingestion of a therapeutic dose. Peak plasma levels occur approximately 0.5–1.0 h after ingestion of therapeutic amounts of immediate-release products but may be delayed 2–4 h after large ingestions. Peak levels may occur even later after ingestion of toxic amounts of extended-release products (e.g.,

Tylenol Arthritis Extended Relief caplets) or products containing diphenhydramine which slow gastric motility (Tylenol PM Extra-Strength) [5, 6]. Once absorbed, acetaminophen is distributed throughout the body water. Protein binding is less than 50 %.

Acetaminophen is metabolized in the liver (96 %) with only 2–4 % excreted unchanged in the urine [7]. Metabolism of therapeutic doses via glucuronidation and sulfation results in the formation of benign metabolites (90–95 %). Oxidation through the cytochrome P-450 enzyme system (CYP 3A4 and CYP 2E1) results in the formation of the toxic metabolite *N*-acetyl-*p*-benzoquinoneimine (NAPQI) (5–10 %). NAPQI is rapidly conjugated with glutathione to form a nontoxic metabolite. The metabolites are excreted in the urine along with the small amount of unchanged drug.

Acetaminophen metabolism in children younger than 6 years of age appears to differ from that in older children and adults, as evidenced by lower levels of hepatotoxicity with toxic plasma levels from single doses. Although young children have more CYP 3A4 enzyme than adults and may form more NAPQI, they have a greater activity of glutathione replacement and can eliminate NAPQI more readily [8]. Once approximately 70 % of glutathione stores are depleted, levels of NAPQI increase, resulting in hepatocyte destruction. Acetylcysteine (Mucomyst), the treatment of choice for toxic acetaminophen ingestions, exerts its protective effect by replacing the depleted glutathione stores and increasing acetaminophen metabolism through benign pathways.

Several risk factors result in increased NAPQI formation and hepatotoxicity, the first being large ingestions of APAP. "Toxic" doses are considered to be >7.5 g in adults and >150 mg/kg in children. However, supratherapeutic doses (>50–75 mg/kg/day) for 1–5 days in children have been shown to cause hepatotoxicity and death. This occurs more often in children ≤2 years of age who have not eaten for a prolonged period. This also can occur in a febrile child with viral gastroenteritis who is not eating and has received several doses of APAP to lower the fever. Parents using adult-strength APAP products instead of the child products may further increase this risk [9].

Risk factors seen in adults include malnutrition, long-term use of acetaminophen, and chronic alcohol consumption, which also deplete glutathione stores. Medications that induce the CYP 3A4 enzyme (carbamazepine, phenobarbital, phenytoin, rifampin) will further increase the formation of NAPQI. All risk factors must be considered in the prevention and treatment of APAP poisoning.

Clinical Presentation

The clinical course of acetaminophen toxicity consists of four stages [10]. Stage 1 is seen within the first 24 h after ingestion, and in older children and adults, it consists of nausea, vomiting, diaphoresis, and malaise. Children under 6 years of age seem to vomit earlier and at lower serum acetaminophen levels. Hepatic enzymes are usually not elevated unless there are other causes of hepatic dysfunction. Severe symptoms including coma indicate extremely large ingestions or co-ingestants.

Stage 2 occurs 24–48 h after ingestion and is characterized by the appearance of laboratory abnormalities indicating hepatic damage and necrosis. The aspartate transaminase [AST, serum glutamic-oxaloacetic transaminase (SGOT)], alanine transaminase [ALT, serum glutamic-pyruvic transaminase (SGPT)], and bilirubin levels begin to rise; with severe toxicity the prothrombin time (PT) is increased. The nausea, vomiting, diaphoresis, and malaise encountered during stage 1 typically subside, although complaints of right upper quadrant pain may be encountered.

Stage 3 is seen 3–4 days after ingestion and reflects maximal hepatic damage. Nausea, vomiting, and malaise reappear and with severe poisonings may be accompanied by jaundice, confusion, somnolence, and coma. Renal, pancreatic, and cardiac damage may also occur. Peak AST, ALT, bilirubin, and PT values occur during this stage. Although AST levels over 1000 IU/L are diagnostic for acetaminophen-induced

hepatotoxicity, levels as high as 30,000 IU/L may be found with severe poisonings. Bilirubin levels exceeding 4 mg/dL, and PT values more than 2.2 times control are indicative of serious hepatotoxicity.

Stage 4 occurs in survivors 7–8 days after ingestion and represents resolution of the hepatic damage. Clinical signs of hepatic dysfunction and enzyme abnormalities have nearly or completely resolved. Permanent hepatic damage is infrequent.

Infrequently, patients suffer hepatic damage following ingestion of "nontoxic" amounts of acetaminophen (see section "Pharmacokinetics") and may present initially at any stage of toxicity. Abnormally high hepatic transaminase levels for the clinical situation are often seen. At risk are those who regularly drink large amounts of alcohol, take acetaminophen long term, are malnourished, or take other drugs that affect hepatic metabolism.

Despite the potential for hepatotoxicity, fewer than 1 % of adult patients develop fulminant hepatic failure, and it is almost never seen in children under 6 years of age. In fact, hepatic abnormalities are seen in fewer than 5 % of children under 6 years of age who have toxic plasma acetaminophen levels.

Diagnosis

The patient's history of medication ingestion is often inaccurate and may omit co-ingestants. The absence of specific clinical signs and symptoms can also be misleading, particularly early in stage 2 when laboratory findings that indicate hepatic damage are minimal and the clinical symptoms seen in stage 1 are abating. A high level of suspicion is helpful particularly in those who are malnourished, consume alcohol on a chronic basis, and are on CYP 3A4 enzyme-inducing medications.

Therefore, plasma acetaminophen levels should be obtained 4 h (possibly at 2 h if ingestion of a liquid with APAP only) or longer after ingestion from all patients with known or suspected acetaminophen overdoses. Acetaminophen levels should also be obtained for *all* ingestions undertaken as a suicide attempt given the risk of co-ingestion of various substances including acetaminophen. The plasma level is then plotted on the Rumack–Matthew nomogram (Fig. 1) and a decision made regarding the need for treatment.

Management

Treatment of acetaminophen poisoning embodies three principles: preventing absorption of ingested acetaminophen from the GI tract, appropriate use of the antidote *N*-acetylcysteine (NAC), and supportive care. Preventing absorption from the GI tract is described under "General Treatment Measures." Activated charcoal should be given in most cases of acute poisoning, within 1 h of acetaminophen ingestion for best results and preferably at least 1 h before NAC administration. Untreated patients seen within 1 h of ingestion are candidates for gastric lavage. The value of emptying the stomach with ipecac is doubtful, and aggressive use of ipecac may cause prolonged vomiting, thereby expelling the oral NAC as well. If a patient has consumed ipecac, activated charcoal should be given not less than 1.0–1.5 h after ipecac administration (and only if vomiting has stopped) because of the risk of aspiration.

Plasma acetaminophen concentrations should be measured 4 h or more after ingestion in all patients. A full course of NAC treatment is indicated for initial levels in the "possible risk" or higher ranges on the Rumack-Matthew nomogram (Fig. 1) regardless of the type of acetaminophen ingested (immediate- or extended-release products). If the concentration is below the possible risk level and the ingested acetaminophen is known to be an immediate-release product, further evaluation and treatment are unnecessary. If the type of acetaminophen ingested is unknown or includes an extended-release product, it is recommended that a second acetaminophen level be determined 4–6 h after the first level. If the second level is higher than the first level or is close to the possible risk level on the nomogram, it is prudent to measure additional acetaminophen levels every 2 h until the levels stabilize or

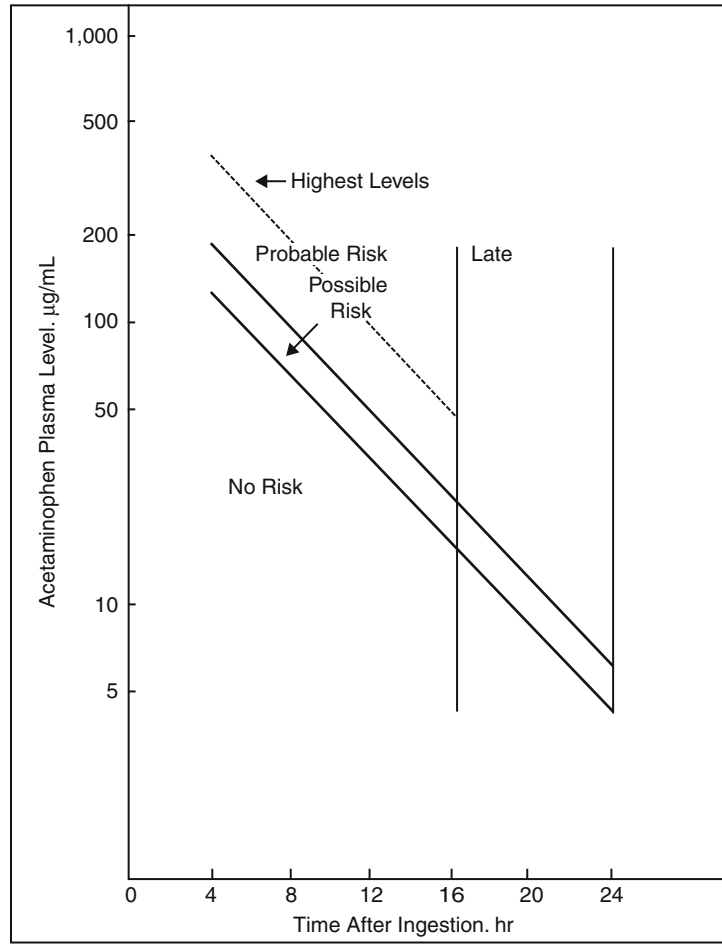

Fig. 1 Rumack–Matthew nomogram (From Rumack et al. [10], with permission)

decline. A full course of NAC treatment should be given if a repeat concentration is in the possible risk or higher ranges on the nomogram. If the concentration remains below the possible risk level, treatment is not indicated.

For optimal therapeutic effect, NAC should be given within 8 h of the toxic ingestion (simultaneously with activated charcoal if necessary to achieve treatment during this period) [11]. If serum levels are not immediately available 8–16 h after ingestion, NAC is given empirically. If the initial and repeat (when indicated) serum concentrations return at nontoxic levels, the NAC may be discontinued in most cases. Possible exceptions include patients at risk for hepatic damage at normal or slightly elevated serum concentrations, including those who regularly drink large amounts of alcohol and those who are severely malnourished. NAC therapy may be effective up to 36 h or more after ingestion, particularly in patients with fulminant hepatic failure [7, 12].

N-acetylcysteine is given orally in a loading dose of 140 mg/kg, followed by 70 mg/kg every 4 h for 17 additional doses. Although activated charcoal adsorbs NAC in vitro, it appears to have a small effect on NAC in vivo, and there are no data showing that activated charcoal inhibits the antidotal efficacy of NAC. Therefore, most information supports the immediate use of activated charcoal with administration of NAC 1 h afterward. If the patient vomits within 1 h of administration of any dose, the dose is repeated. NAC has an odor similar to that of rotten eggs and can be diluted in fruit juices or carbonated beverages to a concentration of approximately 5 % to prevent

nausea and vomiting. Placement of a nasogastric tube may be necessary in cases of refractory vomiting.

Intravenous NAC has been used extensively for treatment of acetaminophen poisoning in Great Britain and Canada, but it is not approved for use in the United States. Intravenous regimens commonly used include a 20-h regimen with a loading dose of 150 mg/kg over 15 min followed by 50 mg/kg over 4 h, then 100 mg/kg over the next 16 h, or a 48-h regimen with a loading dose of 140 mg/kg followed by 70 mg/kg every 4 h for 12 doses [7, 13]. Intravenous administration of oral NAC through millipore filters has been described for situations when intravenous preparations of NAC are not available [14].

Supportive care is often necessary after gastrointestinal decontamination and administering NAC. AST, ALT, bilirubin, PT, complete blood count (CBC), and creatinine values are followed daily until improvement is noted. Treatment for hepatic insufficiency is initiated as indicated.

Cyclic Antidepressants

The 1999 AAPCC TESS identified antidepressants as the poison category associated with the second largest number of deaths that year, after analgesics. Antidepressant poisonings were responsible for the third highest percentage of deaths among categorical exposures, following only stimulants/street drugs and cardiovascular drugs [1]. Cyclic antidepressants (CAs) accounted for only 20 % of antidepressant exposures, but 67 % of deaths. Conversely, selective serotonin reuptake inhibitors (SSRIs) represented 41 % of exposures and 14 % of deaths. The SSRIs are as efficacious as CAs for treatment of depression and are considered first-line therapies for social anxiety disorder, obsessive–compulsive disorder, and panic disorder [15–18]. Despite their low safety profile, CAs continue to be indicated in selected patients for a variety of conditions, including depression, enuresis, and chronic pain (Table 2) (see chapters "▶ Selected Problems of Infancy and Childhood", "▶ Anxiety Disorders," and "▶ Care of the Difficult Patient").

Table 2 Cyclic antidepressants

Generic name	Brand name
Tricyclics	
Amitriptyline	Elavil
	Endep
Amoxapine	Asendin
Clomipramine	Anafranil
Desipramine	Norpramin
Doxepin	Adapin
	Sinequan
Imipramine	Tofranil
Nortriptyline	Pamelor
Protriptyline	Vivactil
Trimipramine	Surmontil
Tetracyclic	
Maprotiline	Ludiomil
Selective serotonin reuptake inhibitors (SSRIs)	
Fluoxetine	Prozac
Paroxetine	Paxil
Sertraline	Zoloft
Fluvoxamine	Luvox
Citalopram	Celexa
Escitalopram	Lexapro

Pharmacokinetics

Cyclic antidepressants are rapidly and completely absorbed when therapeutic amounts are ingested, with peak plasma levels occurring 2–6 h after therapeutic doses. In overdose situations, the severe anticholinergic effects of the CAs result in delayed gastric emptying. Once absorbed, CAs are highly protein bound to plasma proteins (>90 %) and tissue proteins [19]. The remaining unbound compounds readily accumulate in various body tissues (myocardium, liver, brain) at 5–30 times the plasma concentration. The fraction of unbound drug increases as the plasma pH decreases, allowing the antidepressants to accumulate in the tissues and produce toxic effects.

Metabolism of CAs occurs primarily in the liver (90–95 %) and results in the formation of active and inactive metabolites. Metabolites are excreted in the urine and stool. Less than 5 % of CAs or their active metabolites are excreted unchanged. Because of enterohepatic

recirculation and variations in metabolism, the normal half-life for therapeutic doses of CAs ranges from 18 to 36 h. With overdoses the combination of delayed gastric emptying and enterohepatic recirculation leads to increased serum concentrations of CA with half-lives prolonged to >80 h. Plasma drug levels also vary greatly regardless of the dose ingested.

Metabolism of CAs may be affected by patient age and concurrent medications. Consequently, elderly patients typically have a prolonged CA half-life, whereas the converse occurs in children. CA half-lives are shortened by co-ingestions of ethanol, barbiturates, lithium, and tobacco and are prolonged by steroids, oral contraceptives, and phenothiazines, and benzodiazepines.

The SSRIs are almost exclusively eliminated by hepatic metabolism, with all SSRIs (except paroxetine) having active metabolites contributing to serotonergic activity. SSRIs can inhibit hepatic enzymes CYP 3A4 and CYP 2D6 increasing the serum concentrations of several medications (alprazolam, tricyclic antidepressants, propoxyphene, venlafaxine, trazodone) that can further increase toxicity in overdose situations [20].

Clinical Presentation

Overdoses of CAs affect the parasympathetic, cardiovascular, and central nervous systems. Clinical signs and symptoms are the result of several pharmacologic actions including neurotransmitter reuptake inhibition of norepinephrine, dopamine, and serotonin, α-adrenergic blockade, anticholinergic effects, and blockade of myocardial fast sodium channels producing the quinidine-like effect on the myocardium [21]. The signs and symptoms of CA overdose are summarized in Table 3, with most fatal overdoses resulting from cardiac complications. CA overdose should be suspected in any patient (child or adult) who presents with signs of anticholinergic poisoning, seizures, coma, hypotension, respiratory depression, or arrhythmias [22].

Signs and symptoms of an overdose are variable and may change rapidly. Findings resulting from the anticholinergic effects (dilated pupils, dry mouth, hyperpyrexia, blurred vision, CNS excitability) are typically the first to appear. Depending on the time since ingestion, however, patients may present as asymptomatic, have mild to moderate anticholinergic effects, or exhibit signs of severe toxicity including seizures, coma, arrhythmias, and cardiac arrest. Symptoms rapidly progress, with seizures and ventricular

Table 3 Signs and symptoms of cyclic *antidepressant overdose*

Central nervous system
Sedation
Restlessness
Confusion
Ataxia
Nystagmus
Dysarthria
Hallucinations
Myoclonus
Seizures
Respiratory depression respiratory arrest coma
Additional anticholinergic effects
Mydriasis (dilated pupils)
Blurred vision
Dry mouth
Hyperpyrexia
Hypoactive bowel sounds
Urinary retention
Cardiovascular system
Sinus tachycardia
Prolonged QRS, PR, QTc intervals
Rightward-terminal 40-ms frontal plane axis deviation of QRS
Bundle branch block (especially RBBB)
Second- or third-degree AV block
Intraventricular conduction delays
Arrhythmias (atrial and ventricular)
Hypotension
Congestive heart failure
Cardiac arrest
Miscellaneous effects
Adult respiratory distress syndrome
Renal tubular acidosis
Metabolic acidosis

RBBB right bundle branch block, *AV* atrioventricular

arrhythmias typically occurring within 6 h after ingestion [23].

Sinus tachycardia is frequently present with serious CA overdoses but is a nonspecific finding. A limb-lead electrocardiographic (ECG) QRS interval of more than 0.10 s is more specific and is considered a sign of potentially serious toxicity [21, 23]. A rightward shift in the terminal 40-millisecond QRS frontal plane axis and R wave $\geq$3 mm in lead AVR are also commonly associated with CA toxicity and considered to be a more significant predictor for seizures or dysrhythmias [21, 24].

Cyclic antidepressants have a low therapeutic index (median toxic dose divided by median effective dose). Whereas doses of 1–4 mg/kg may be therapeutic, overdoses as small as 20 mg/kg may be fatal. For example, ingestion of four 100-mg tablets could be fatal if ingested by a 20-kg child, and ingestion of a 2-week supply of 100 mg tablets can be fatal for an adult.

Overdoses of SSRIs are considered much less lethal than CA and the actual fatality rate due to SSRIs overdose alone is not clear due to the effects of co-ingestants in many patients. The toxic effects of SSRI overdose stem from the effects of excess serotonin (5-hydroxytryptamine, 5-HT) on multiple receptors. Stimulation of 5-HT_1, 5-HT_2, and 5-HT_3 receptors, as well as the resulting inhibition of dopamine release, produces many of the symptoms seen in toxic situations [20].

Patients can experience minor symptoms such as drowsiness, nausea, vomiting, and/or tremors when ingesting doses 50–75 times the normal daily dose of SSRIs. Higher doses (150 times the normal daily dose) can result in severe toxicity or death. Patients may experience "serotonin syndrome" if they present with three or more of the following: mental status changes, diaphoresis, myoclonus, diarrhea, fever, hyperreflexia, tremor, or incoordination. Patients can also experience tachycardia, QT prolongation, and seizures. Many patients experiencing toxicity have co-ingested ethanol, benzodiazepines, or serotonergic agents (dextromethorphan, tricyclic antidepressants) [15, 20].

Diagnosis

A comprehensive history and physical examination (Table 3) should alert the clinician to the possibility of CA overdose. The diagnosis can be confirmed by blood or urine screens for the presence of CAs or SSRIs. Although plasma levels are useful for confirming the diagnosis, they are of little help in predicting serious toxicity.

Co-ingestions of other drugs and the presence of preexisting heart disease must be considered when evaluating patients for CA or SSRI overdose. Each may complicate the clinical presentation and result in a delay in diagnosis.

Management

Treatment of CA poisoning embodies four general principles: preventing absorption of ingested CA from the GI tract, supportive (especially circulatory and respiratory) care, seizure management, and control of arrhythmias. Absorption from the GI tract should be prevented via gastric lavage and use of activated charcoal, as described above (see section "General Treatment Measures"). Ipecac is contraindicated because vomiting may delay charcoal administration or cause aspiration of vomitus in patients with rapidly changing sensoriums.

Asymptomatic patients without signs of CA overdose and with QRS intervals of less than 0.10 s, no QT prolongation, and no deviation of the terminal portion of the QRS (R wave $<$3 mm in AVR) may be transferred for psychiatric management after being closely observed in the emergency room for a minimum of 6 h. Patients showing initial signs and symptoms of CA toxicity and patients with QRS or QT prolongation or deviation of the R wave in AVR should be admitted to the intensive care unit (ICU) and monitored until signs and symptoms of toxicity (including ECG abnormalities) resolve. Patients with refractory or prolonged signs of toxicity should remain in the ICU until 24 h after resolution of all toxic manifestations.

Aggressive supportive care is essential for managing CA poisoning. Patients with depressed

mental status should be evaluated for other possible etiologies. Where appropriate, the patient is intubated with a cuffed endotracheal tube to secure the airway and prevent impending respiratory failure or aspiration. Intravenous access should be established and isotonic fluids administered to correct hypotension and restore effective blood volume. If signs of cardiotoxicity are present (QRS $\geq$0.10 s, R in AVR $\geq$3 mm, QT prolongation, right bundle branch block, wide-complex tachycardia), intravenous $NaHCO_3$ boluses of 1–2 mEq/kg given over 1–2 min can be used until signs of cardiotoxicity and the hypotension improve. An infusion of 150 mEq of $NaHCO_3$ in 1 L of 5 % dextrose in water is then given to maintain an arterial pH of 7.45–7.55 [25]. Patients unable to tolerate large amounts of intravenous sodium may be treated with mechanical ventilation, although this is not as effective as $NaHCO_3$ administration.

Hypotension refractory to crystalloid and sodium bicarbonate therapy may be treated with vasopressors such as norepinephrine or dopamine [25, 26]. Dopamine may be less effective than norepinephrine in treating refractory hypotension from CA overdoses when given at the usual doses, but use at a high dosage (up to 30 μg/kg/min) may improve the response rate in resistant cases. Dobutamine can be used to treat hypotension associated with myocardial depression but causes hypotension in some patients.

Seizures may be treated immediately with intravenous diazepam (Valium) 0.15 mg/kg at 15–20-min intervals until seizures are controlled or to a total dose of 30–40 mg. This regimen is followed by treatment with an anticonvulsant with a longer half-life, such as phenobarbital. Although recommended as second-line therapy, phenobarbital can cause respiratory depression and acidosis and must be used with caution [27]. Phenytoin (Dilantin) should be avoided because of potential cardiotoxicity. Although physostigmine has been advocated for the treatment of anticholinergic CNS effects, it has considerable cardiac and CNS toxicity and should not be used in CA overdoses.

Arrhythmias induced by CAs are treated by sodium bicarbonate therapy and alkalinization of the plasma to pH 7.45–7.55, the use of antiarrhythmics, and cardioversion when necessary. If serious ventricular arrhythmias persist following alkalinization and other supportive measures, lidocaine is the initial drug of choice [25, 28] (see chapter "▶ Ocular Trauma"). The use of class IA (quinidine, procainamide, disopyramide) and IC (flecainide, encainide, propafenone) antiarrhythmic agents is contraindicated because they also inhibit the myocardial fast sodium channels and worsen the cardiotoxicity.

Treatment of SSRI intoxication includes gastric decontamination (activated charcoal) and supportive care for seizures or cardiovascular manifestations as necessary. Treatment for serotonin syndrome includes supportive therapy, cooling blankets, ice packs or ice water enemas, and the use of dantrolene and cyproheptadine in a manner similar to that used in treating neuroleptic malignant syndrome.

Aspirin/Salicylates

Poisoning by ingestion of oral salicylate-containing medications remains a serious problem in the United States. According to US poison control center data, there were more than 16,300 exposures to aspirin and combination products containing aspirin that necessitated poison control center contacts in 1999 [1]. Approximately 28 % of exposures were in children younger than 6 years of age, 32 % in those 6–19 years, and 40 % in adults older than 19 years. There were 51 deaths in all categories of exposure. By 2012 [1]a, the numbers changed significantly. No deaths were reported by salicylates in children younger than 6 years of age. In the remaining groups, age 6–12 years, there was only 1 reported death by salicylate poisoning out of 7 fatal exposures. In the age range 13–19 years, there were 3 fatal salicylate poisonings out of 45 reported fatalities.

Pharmacokinetics

Salicylates are rapidly absorbed from the stomach, jejunum, and small intestine. Peak plasma salicylate concentrations are achieved 0.5–2.0 h after ingestion of immediate-release preparations and usually 4–6 h or more after ingestion of extended-release enteric-coated tablets [29]. With large ingestions, absorption and subsequent peak plasma levels may be delayed as much as 8–12 h because of decreased gastric emptying. In addition, large ingestions are often absorbed more slowly because clumps of aspirin tablets form concretions in the stomach resulting in salicylate in the stomach long after ingestion. Consequently, peak levels may occur 24 h or more after ingestion of large amounts of extended-release tablets.

Following absorption of therapeutic doses, aspirin is rapidly hydrolyzed to salicylic acid, and both compounds are highly protein bound (80–90 %) to albumin. Distribution throughout body fluids is extensive and largely dependent on the amount of salicylate ingested and the pH of the body fluids. The amount of pharmacologically active free salicylate increases as salicylate levels increase above the therapeutic range.

Free salicylate exists in either ionized or nonionized form, the nonionized form being able to readily diffuse into body tissues. Decreased body fluid or tissue pH results in increased relative amounts of the nonionized salicylate, allowing greater tissue penetration. Consequently, large overdoses (with greater amounts of free salicylate) in conditions associated with metabolic acidosis (dehydration, chronic or large salicylate overdoses, sepsis) often result in large tissue and CNS concentrations and hence greater toxicity. Also, alkalinizing the urine increases the concentration of ionized form in the urine, thereby reducing the amount of salicylate that is reabsorbed.

After therapeutic doses, salicylic acid is eliminated unchanged in the urine (5–10 %) or as one of five metabolites (90–95 %). At higher doses metabolic pathways are saturated, resulting in exponential increases in plasma salicylate levels. For example, an increase in daily aspirin dose from 65 to 100 mg/kg increases the serum concentration 300 % [30].

Clinical Presentation

The actions of salicylates that account for most of the signs and symptoms seen with poisonings include the following: (1) direct stimulation of the CNS respiratory center, producing respiratory alkalosis and initial compensatory renal excretion of HCO_3; (2) uncoupling of oxidative phosphorylation with increased catabolism, increased oxygen utilization, and increased CO_2 production, an action that can result in metabolic acidosis and hyperpyrexia (tissue glycolysis and utilization of glucose are also increased); (3) inhibition of Krebs cycle dehydrogenases, leading to increased amounts of pyruvic acid and lactic acid; (4) stimulation of gluconeogenesis; (5) increased lipolysis and lipid metabolism with formation of ketones, acetoacetic acid, β-hydroxybutyric acid, and acetone; (6) inhibition of aminotransferases, resulting in increased plasma amino acids and aminoaciduria; (7) irritation of the gastric mucosa and stimulation of the chemoreceptor trigger zone, with subsequent nausea and vomiting; and (8) altered coagulation and hemostasis via cyclooxygenase inhibition and decreased platelet aggregation, increased capillary fragility, thrombocytopenia, and hypoprothrombinemia.

The predominant clinical effects of salicylate poisoning can be grouped into two general categories: acid–base and fluid–electrolyte abnormalities. Approximate guidelines correlating the amount of salicylate ingested to the symptoms produced are as follows:

<150 mg/kg – minimal symptoms
150–300 mg/kg – moderate symptoms
300–500 mg/kg – severe symptoms
>500 mg/kg – potentially fatal

Minimal symptoms include mild to moderate hyperpnea, sometimes with lethargy. Moderate symptoms are characterized by severe hyperpnea and CNS signs including lethargy, excitability, or

both. Severe symptoms include severe hyperpnea, semicoma, coma, and convulsions [31].

Signs and symptoms, which usually begin within 3–8 h of ingestion, include nausea and vomiting, hyperpnea, and respiratory alkalosis. The respiratory alkalosis typically persists but is accompanied by progressive metabolic acidosis as the severity and duration of the poisoning increases. Additional findings may include tinnitus, disorientation, and hyperpyrexia. Cumulative GI, renal, pulmonary, and skin losses of fluids can be massive and may result in hypovolemia, oliguria, and renal failure. Hypernatremia, hyponatremia, and hypokalemia are frequently seen. Initial hyperglycemia may be followed by hypoglycemia caused by depletion of tissue glucose stores. Signs of CNS hypoglycemia, including lethargy, coma, and seizures, may occur despite normal plasma glucose levels [32]. Unexpected bleeding and hepatotoxicity are uncommon.

The progression of signs and symptoms is increased in young children, with large ingestions, with illnesses that include dehydration, and with chronic exposures. Also, use of therapeutic doses of salicylates for conditions accompanied by dehydration and acidosis may result in greater tissue (i.e., CNS) concentrations and increased morbidity and mortality, despite relatively low blood salicylate concentrations.

The clinical presentation of patients with chronic salicylate intoxication may differ from that of patients with acute intoxication. Potential differences include a more gradual onset of symptoms, an advanced stage of intoxication at initial presentation, and a predominance of neurologic symptoms particularly in the elderly [33]. Neurologic findings may include confusion, agitation, stupor, paranoia, and bizarre behavior. Chronic salicylism has been misdiagnosed as sepsis, alcohol withdrawal, myocardial infarction, organic psychosis, and dementia.

Salicylate-induced noncardiogenic pulmonary edema and the adult respiratory distress syndrome are complications of salicylate ingestion, particularly chronic ingestions [34]. Risk factors include increased age, cigarette smoking, and concurrent medical illnesses. Chronic salicylate intoxication has also been associated with development of a pseudosepsis syndrome characterized by hyperthermia, leukocytosis, hypotension with decreased systemic vascular resistance, and multiple organ failure [35].

Diagnosis

A history of salicylate ingestion helps confirm the clinical impression, but documentation of toxic serum salicylate levels is essential for establishing the diagnosis. The Done nomogram (Fig. 2) is used to assess the significance of serum salicylate levels following acute ingestions [31]. Blood salicylate levels should be determined 6 h or more after the acute ingestion. By plotting the serum level at a given time after ingestion, it is possible to predict the severity of the poisoning and the expected symptoms. This nomogram is most useful for acute ingestions and may underestimate the severity of poisonings after chronic exposures, in patients with illnesses accompanied by dehydration and acidosis, in cases of ingestion of enteric-coated or sustained-release products, and in those with indeterminate times of ingestion. Therefore serial serum salicylate levels every 1–2 h after the initial salicylate level have been recommended until levels decline and the patient's condition stabilizes [36].

Management

Treatment of salicylate poisoning encompasses three principles: preventing absorption of ingested salicylate from the GI tract; treating any fluid, electrolyte, or metabolic derangements; and enhancing elimination of salicylate from the body. Careful monitoring of the acid–base status, including prevention of worsening acidosis (respiratory or metabolic), is essential. Preventing absorption from the GI tract (described under "General Treatment Measures") includes emesis and/or gastric lavage (depending on the necessity for gastric emptying) and administering activated charcoal to increase elimination.

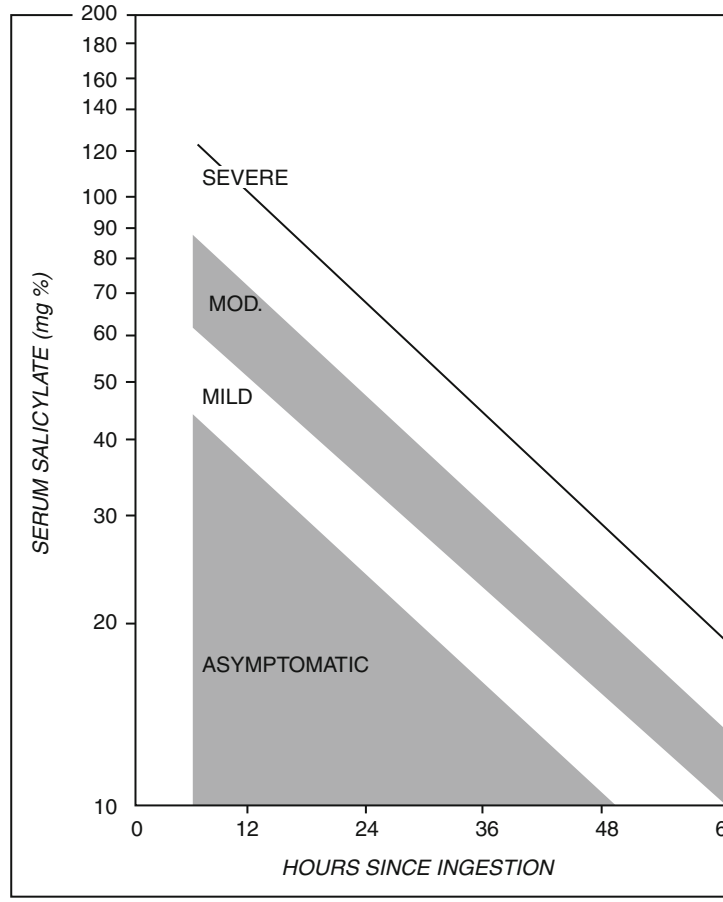

Fig. 2 Done nomogram (From Done AK. Pediatrics 1960;26:800–7, with permission)

Fluid resuscitation is initially directed toward restoring an effective blood volume. If hypotension is present, an isotonic solution should be given intravenously until the patient is no longer orthostatic. If hyperglycemia is not a problem, the solution should contain at least 5 % dextrose. If dextrose is not desired, normal saline or a mixture of 0.45 % NaCl with one ampule of sodium bicarbonate (total 50 mEq $NaHCO_3$) at 10–15 mL/kg/h for 1–2 h may be used, depending on the presence and degree of acidosis. Subsequent fluid management is directed toward alkalinizing the urine, preventing CNS hypoglycemia, and treating electrolyte and fluid abnormalities.

An effective alkaline diuresis (urine pH >7.5) to enhance salicylate excretion should be attempted once the patient is no longer orthostatic and urine output has been established. Superiority of a single method to achieve this has not been established. An initial bolus of $NaHCO_3$, 2 mEq/kg intravenously, followed by an infusion of 1000 cm^3 of dextrose 5 % in water (D_5W) plus three ampules of $NaHCO_3$ (50 mEq $NaHCO_3$/ampule) at 1.5–2 times maintenance rate has been effective. Potassium should be added to the IV as needed for potassium levels below 4.0 mEq/L. Frequent monitoring of serum electrolytes and glucose is essential. The urine pH should be checked hourly until stable at >7.5. Arterial blood gases should be monitored 2–4 h into treatment to ensure the blood pH is *no more than* 7.5. Alkalinization can be discontinued when the serum salicylate level is within the therapeutic range.

Hemodialysis is indicated for unresponsive or worsening acidosis, acute and chronic poisonings with salicylate levels of >100 mg/dL and 40–60 mg/dL, respectively, renal or hepatic

Table 4 Commonly prescribed benzodiazepines

Generic name	Brand name
Alprazolam	Xanax
Chlordiazepoxide	Librium
Clonazepam	Klonopin
Clorazepate dipotassium	Tranxene
Diazepam	Valium
Estazolam	ProSom
Flurazepam	Dalmane
Lorazepam	Ativan
Midazolam	Versed
Oxazepam	Serax
Quazepam	Doral
Temazepam	Restoril
Triazolam	Halcion

failure, noncardiac pulmonary edema, and persistent, severe CNS symptoms [31, 36]. Additional supportive care may be necessary depending on the severity of the poisoning and the patient's response to therapy.

Benzodiazepines

Benzodiazepines are widely prescribed for a variety of conditions, including acute anxiety, convulsions, neuromuscular disorders, panic attacks, insomnia, alcohol withdrawal, and induction of anesthesia. They are commonly used in inpatient and outpatient settings to produce conscious sedation for minor surgical procedures. US Poison Control Center data from 2012 indicate that benzodiazepines accounted for 46 % of all sedative deaths (51 of 110 total deaths) [1]a. Because this information does not include poisonings seen in other health care facilities, it is likely that the total number of benzodiazepine overdoses in the United States was considerably greater. Commonly used benzodiazepines are listed in Table 4.

Pharmacokinetics

Most benzodiazepines are rapidly and completely absorbed following an oral dose. Peak plasma levels occur 0.5–3.0 h after ingestion of therapeutic doses but may be delayed after large overdoses or when co-ingested with alcohol or antacids. Once absorbed, benzodiazepines are extensively bound to serum proteins (70–99 %), with the unbound drug being the active form. Conditions associated with hypoalbuminemia (e.g., cirrhosis) result in a greater proportion of unbound drug and may cause an increased frequency of side effects.

Benzodiazepines have a large volume of distribution in the body, with concentrations in the brain, liver, and spleen being greater than unbound drug concentrations in the blood. The duration of action depends on the rate and extent of tissue distribution (lipid solubility) as well as the rate of elimination.

Benzodiazepines are metabolized in the liver primarily by the CYP 3A4 enzyme pathway and to a minor extent the CYP 2C9 pathway resulting in the formation of active and inactive metabolites. Depending on the benzodiazepine ingested, metabolism may be prolonged by advanced age, cirrhosis, and the coadministration of various medications. These include macrolide antibiotics (clarithromycin, erythromycin), calcium channel blockers (diltiazem, verapamil), antifungal agents (fluconazole, itraconazole, ketoconazole), antidepressants (fluoxetine, fluvoxamine, nefazodone), protease inhibitors, and omeprazole. In addition, concomitant ingestion of grapefruit juice and acute alcohol ingestion can increase benzodiazepine serum concentrations [37, 38]. Although differences exist among benzodiazepines, excretion of metabolites and small amounts of unchanged drug (<1 % of the total dose) occurs primarily in the urine.

Clinical Presentation

Benzodiazepines exert their clinical effects by increasing neurotransmission in γ-aminobutyric (GABA)ergic synapses in the CNS. Specific benzodiazepine receptors, associated with GABAergic pathways, are found predominantly in the cerebral cortex, limbic structures, and cerebellum [39, 40]. Because the major CNS inhibitory effect is mediated via GABAergic pathways, benzodiazepine stimulation causes several physiologic effects, including sedation,

anxiolysis, striated muscle relaxation, and anterograde amnesia.

Benzodiazepines have a high margin of safety, and overdoses usually produce only mild to moderate signs of toxicity, including ataxia, dysarthria, drowsiness, and lethargy. However, severe overdoses can cause coma, hypotension, hypothermia, and respiratory distress requiring endotracheal intubation and assisted ventilation or, in select cases, administration of flumazenil [41, 42]. Such complications are rare in benzodiazepine-only ingestions but occur much more frequently with co-ingestions of other drugs that cause CNS depression (especially alcohol) (see chapter "▶ Athletic Injuries"). CNS depression is worsened in the elderly, in those taking large amounts, in patients with chronic diseases, and in those taking medications that impair hepatic benzodiazepine metabolism. Deaths caused by benzodiazepine-only overdoses are rare.

Diagnosis

A complete history and physical examination are important for determining the diagnosis and type of ingested medication. The diagnosis should be confirmed in all patients by blood or urine screens for the presence of benzodiazepines. It is important to screen routinely for the presence of co-ingestants, particularly in comatose patients. Quantitative determinations of blood benzodiazepine levels are not useful for the management of benzodiazepine overdoses because blood concentrations do not correlate well with clinical manifestations [43, 44].

Management

Treatment of benzodiazepine overdoses consists of patient stabilization, preventing absorption of ingested benzodiazepines from the GI tract, and supportive care including airway support and mechanical ventilation when necessary. Administration of the antidote flumazenil may be useful in selected patients, but is not recommended for routine use in patients with possible mixed drug overdoses or unknown medical histories [45, 46]. Preventing absorption from the GI tract is described above (see section "General Treatment Measures").

Patients are initially assessed for complications from CNS depression. Vital signs are evaluated and the adequacy of the airway and respiratory status ensured. Patients with respiratory depression and hypoxia or hypoventilation are intubated and placed on mechanical ventilation. Comatose patients and others with severe overdoses are examined for evidence of aspiration, hypotension, and hypothermia. Once stabilized, selected patients with benzodiazepine overdose (documented by drug screen or reliable history) who are comatose or have severe CNS depression may be treated with flumazenil (Romazicon). Flumazenil should be avoided in patients suspected of co-ingesting cyclic antidepressants, those with a history of benzodiazepine dependence, or those with a history of seizure disorders treated with benzodiazepines [46–48]. The risks of lethal dysrhythmias, benzodiazepine withdrawal, or seizures outweigh the potential benefits of treatment in these cases.

Flumazenil is a competitive inhibitor of CNS benzodiazepine receptor sites and reverses benzodiazepine-induced CNS depression. Recommended doses for benzodiazepine overdoses in adults are 0.2 mg IV over 30 s; if no response, give 0.3 mg IV over 30 s. Additional doses of 0.5 mg may be given at 1-min intervals as needed up to a total dose of 3 mg. Patients occasionally require a total dose of 5 mg for optimal response, but the requirement for higher dosages may indicate CNS depression due to the presence of co-ingestants [49]. Comatose patients typically awaken within minutes of intravenous administration. The duration of action is approximately 1 h (it may be shorter) and is related to the doses of benzodiazepine ingested and flumazenil administered [39]. Resedation may be observed in cases with prolonged CNS depression and can be treated with repeat 0.2 mg IV boluses (given over 30–60 s) as required, to no more than 3 mg in 1 h. Patients who fail to respond to a maximum dose of flumazenil (5 mg within 5 min) should be

evaluated for co-ingestants and other causes of CNS depression. Flumazenil is not approved for treatment of overdoses in children. For reversal of conscious sedation in children, 0.01 mg/kg (up to 0.2 mg) may be given intravenously over 15 s. If there is no response after 45 s, 0.01 mg/kg (up to 0.2 mg) may be given every 60 s (up to four doses) as needed to a maximum total dose of 0.05 mg/kg (or 1.0 mg, whichever is lower).

The stomach may be evacuated by gastric lavage (regardless of flumazenil administration) if the time since ingestion is less than 1 h, particularly in mixed drug ingestions. Activated charcoal should be administered in most cases and is effective when used as the sole treatment. The use of ipecac should be avoided.

Forced diuresis or efforts to remove the drugs by "cleansing" the vascular compartment (hemodialysis and hemoperfusion) are ineffective and are not indicated for management of overdoses. Antibiotics and corticosteroids are not used except for specific indications.

Supportive care is provided as needed. Hypotension can be managed with crystalloid solutions initially and vasopressors thereafter, as indicated. Treatment of poisoning by co-ingestants is targeted to the specific overdose agents.

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Family Medicine
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Care of Acute Lacerations

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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 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].

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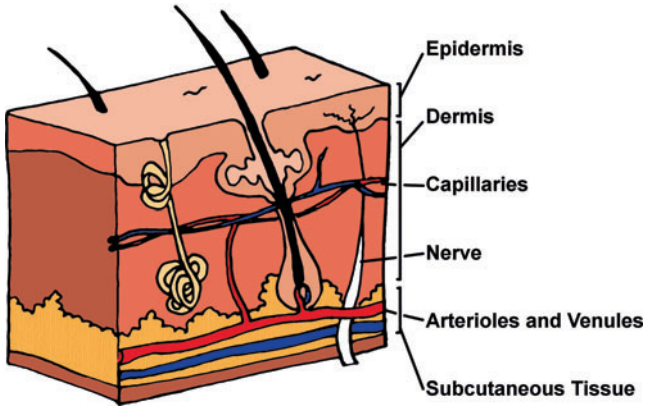

Fig. 1 Normal skin anatomy

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 opened 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 should be loosely approximated with interrupted sutures to 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. 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

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and can be used alone or as an adjunct to injectable agents. Once the wound is anesthetized, distraction with toys or games helps minimize the patient's anxiety.

Injectable Anesthesia

Injectable anesthetics achieve effect more quickly than topical agents but are more painful. The discomfort 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 [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. 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 [7–9].

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).

Procedural Sedation

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. Several terms are used to describe this practice. This text will use the term "procedural sedation and analgesia" (PSA). PSA can be safely utilized by family physicians so long as they are familiar with, and capable of managing, the potential complications associated with the medications required. The goal of PSA in laceration repair is to facilitate patient tolerance of the procedure without compromising

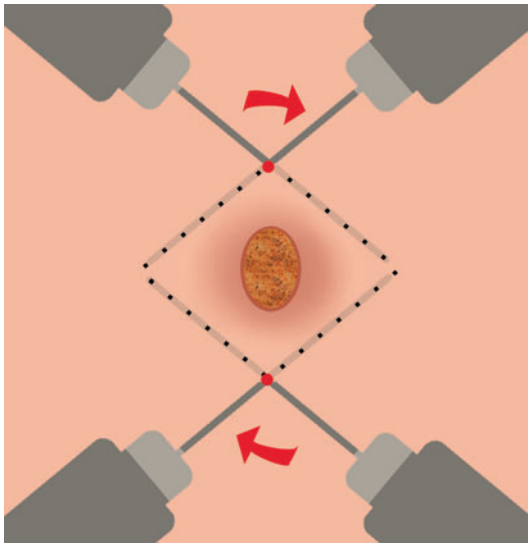

Fig. 2 Injectable anesthesia by field block

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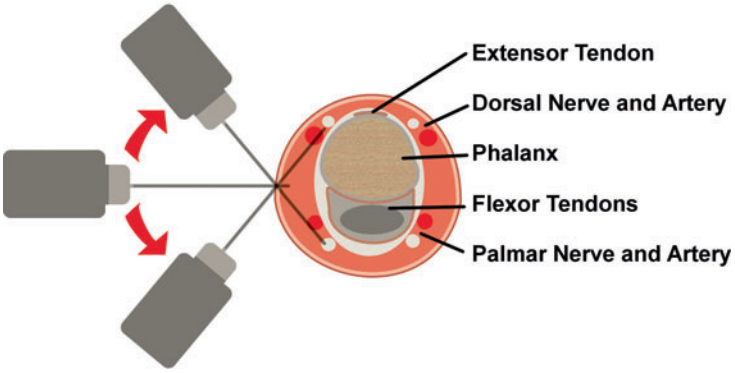

Fig. 3 Digital nerve block

oxygenation or other cardiorespiratory functions. Often patients will maintain the ability to respond to verbal cues; however, occasionally a deeper level of sedation may be required. Many institutions have protocols for PSA; providers are encouraged to consult these if available.

Prior to initiating PSA, patients or their guardians should be informed of the risks of the procedure; the most significant of these are respiratory depression, apnea, hypotension, laryngospasm, vomiting and aspiration; however, other drug-specific effects exist (see Table 1). At a minimum, documentation of verbal consent is recommended. A thorough history and physical exam (including past medical history and review of allergies and medications) is strongly recommended to alert physicians to underlying conditions that may complicate PSA. The physical exam should include assessment of the patient's airway to alert physicians to potential complications should advanced respiratory support be required. While aspiration is a feared complication, delay of PSA based on timing of last oral intake is not necessary [10].

Unplanned complications should be anticipated and appropriate equipment available. Broadly, these should include supplies for additional intravenous access, basic and advanced airway management (including suction), pharmacological antagonists (naloxone and flumazenil), and medications for arrhythmias or other cardiovascular complications. The patient should be placed on supplemental oxygen. Blood pressure and heart rate should be assessed at 5 min intervals and oximetry should be continuous [11]. Capnography, if available, can detect hypoventilation and apnea earlier than pulse oximetry [10]. These data should be recorded and reported to the physician contemporaneous to the procedure. Monitoring should commence prior to sedation and continue through the recovery period (reference). Minimum personnel requirements are the physician performing the procedure and a nurse to administer medications and keep a written record. There are no specific criteria to guide the optimal duration of monitoring following PSA; however, protocols exist at many institutions. At a minimum, patients should be monitored by a trained member of the team (typically a nurse) until the patient is able to independently maintain oxygenation and airway patency. Most often, some form of monitoring is continued until the patient regains his/her baseline level of consciousness. While monitoring a patient undergoing PSA, personnel should not engage in other activities beyond minor, interruptible tasks [11].

Various medications are used for PSA. The most common of these are listed below (Table 1). All doses given are for intravenous administration. The list of considerations highlights only the most common issues. Providers with additional questions or inexperience with these medications should consider consulting a more complete monograph. Impairment of hepatic or renal function as well as body size and composition (i.e., volume of distribution) can all affect the extent and duration of medication effect. Typically, a sedative or anxiolytic is combined with an opiate analgesic. The American Society of Anesthesiologists recommends intravenous administration of medications for PSA though other routes

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Table 1 Medications for PSA

Medication	Dose (IV route)	Onset	Duration	Considerations
Fentanyl (Sublimaze) *Class: Opiate*	Adult 0.5–2 mcg/kg Geriatric 0.25–1 mcg/kg Peds 0.5–2 mcg/kg	Immediate	30–60 min	Impairs respiratory drive Chest wall rigidity (esp in high doses and in children) Reverse with naloxone (Narcan)
Midazolam (Versed) *Class: Benzodiazepine*	Adult 0.5–1 mg given over 2 min Peds <6 months: 50 mcg/kg 6 months to 6 years: 50–100 mcg/kg 6–12 years: 25–50 mcg/kg	3–5 min	30 min	Can cause paradoxical excitement (up to 10–15 % of patients) Reversed with flumazenil (Romazicon) – flumazenil can cause seizures in patients on chronic benzodiazepine therapy
Ketamine (Ketalar) *Class: Dissociative anesthetic*	Adult 1–4.5 mg/kg Peds 1–2 mg/kg	30 s	5–10 min	Absolute contraindication in children <3 months (relative contraindication 3–12 months) Avoid with ocular globe injury and severe hypertension "Emergence phenomenon"
Etomidate (Amidate)	Adult 0.3–0.6 mg/kg Peds <10 years: Do not use >10 years: 0.3–0.6 mg/kg	60 s	3–5 min	Adrenal suppression
Dexmedetomidine (Precedex)	Adult 1 mcg/kg over 10 min Geriatric 0.5 mcg/kg over 10 min Peds Do not use			Hypotension

of administration may be preferable in certain situations; for example, a small child with a relatively minor laceration may be less anxious with an intranasally administered medication. It should be noted that soothing music and visual distraction have both been shown to decrease the need for sedation with unpleasant procedures in adults and children.

Opiates. Opiate medications act on mu receptors to blunt pain response. They can alter consciousness and depress respiratory drive, increasing the risk of hypoventilation and apnea. Their effects are dose dependent and are potentiated by other sedatives and anesthetic agents. The most commonly used opiate for PSA is fentanyl (Sublimaze), an agent with rapid onset and recovery times. In children and in large bolus doses (50 mcg/kg), chest wall rigidity can occur [12].

Benzodiazepines. Benzodiazepines cause sedation and anxiolysis via interaction with GABA receptors. They do not produce analgesia so are typically administered with an opiate. This combination will potentiate the sedation and respiratory depression typically seen with both agents. Midazolam (Versed) is most often used for PSA due to its rapid metabolism and its amnestic effects.

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Ketamine. Ketamine (Ketalar) is a dissociative anesthetic with relatively little effect on hemodynamic and respiratory function. There is an absolute contraindication to ketamine for children less than 3 months old and a relative contraindication in children 3–12 months of age due to risk of laryngospasm. Because ketamine induces catecholamine release, it is contraindicated in patients with acute ocular globe injuries and those with severe hypertension. The most common adverse effect of ketamine is related to its dissociative properties and is known as an "emergence phenomenon." The term refers to profound disorientation as the medication wears off. It occurs in as many as 20 % of patients and is typically more disturbing to adults than children [13]. Adding midazolam to ketamine does not appear to decrease the anxiety provoked by emergence phenomena. Family members of patients should be educated about the effects of ketamine (nystagmus, vacant staring) and encouraged to minimize visual, auditory, and tactile stimulation during the recovery period.

Etomidate. Etomidate (Amidate) is widely used for sedation due to its minimal effects on hemodynamics. It works via a GABA-mediated mechanism. The main adverse effect of etomidate is a transient suppression of adrenal function. For this reason, it is relatively contraindicated in septic patients.

Dexmedetomidine. The newest anesthetic agent in regular use for procedural sedation is dexmedetomidine (Precedex). A potent alpha-2 agonist, dexmedetomidine has potential to induce hypotension but has almost no effect on respiration [12].

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, 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 postrepair 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 physician 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

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Table 2 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)

Table 3 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
Non-absorbable	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

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]. 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 ½ curvature and slides through skin better than a tapered needle (Table 3).

Wound Closure: Principles and Techniques

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

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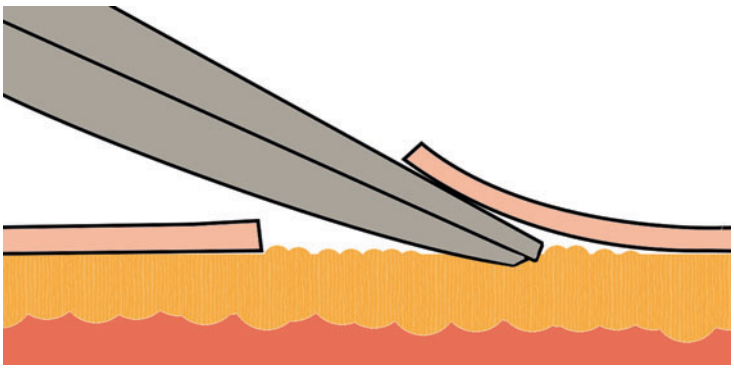

Fig. 4 Undermining wound edges, sagittal view

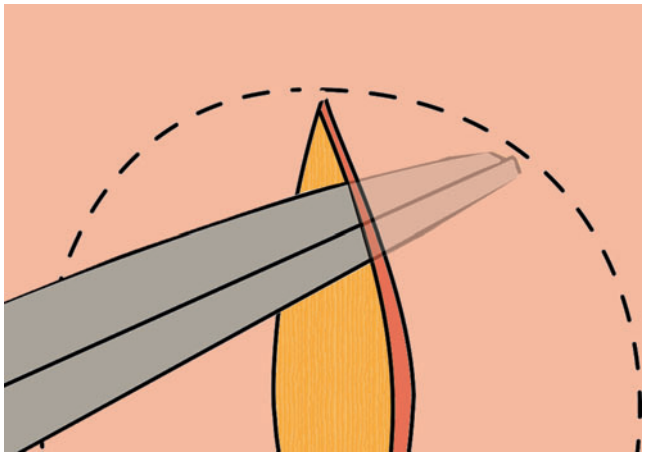

Fig. 5 Undermining wound edges

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].

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. Deep absorbable sutures are used to close this so-called dead space. If deep sutures are insufficient, temporary drains (latex tubing or gauze wicks) are used until the space closes or drainage stops.
3. *Approximation of Tissue Layers:* Sutures should approximate corresponding tissue types with enough pressure to slightly evert 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

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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 stitch should be as wide as it is deep (Fig. 6). Using an instrument tie (Fig. 7), 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. 7).

Simple Running Closure

A simple running closure can be completed quickly, an advantage in emergency situations (Fig. 8). It is useful for long, low-tension wounds but should be avoided in high-tension wounds due to the risk of circulatory compromise. Interrupted 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 [19–21]. Intradermal sutures provide less tissue support than percutaneous sutures so should be reserved for linear, shallow wounds under minimal tension (Fig. 9).

Buried knots are used to anchor absorbable intradermal sutures (Fig. 10). 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.

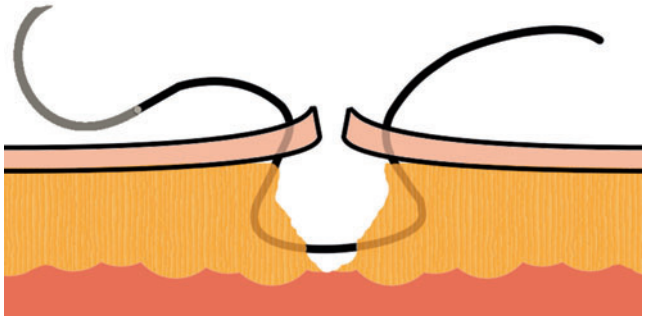

Fig. 6 Simple interrupted, sagittal view

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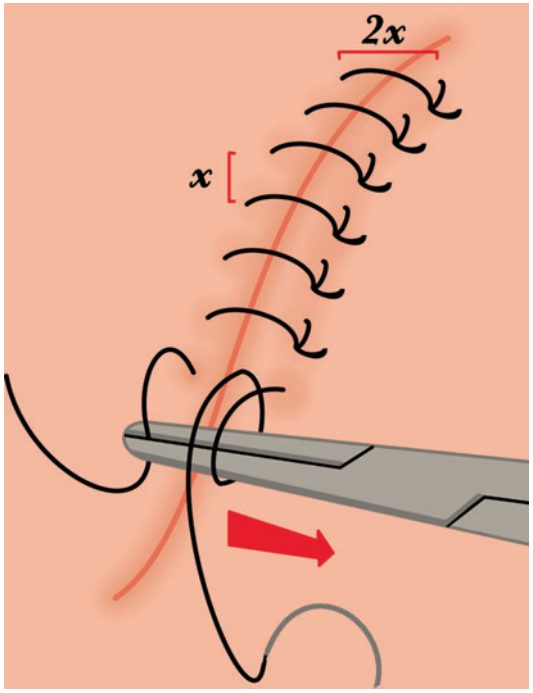

Fig. 7 Suture spacing of simple interrupted closure

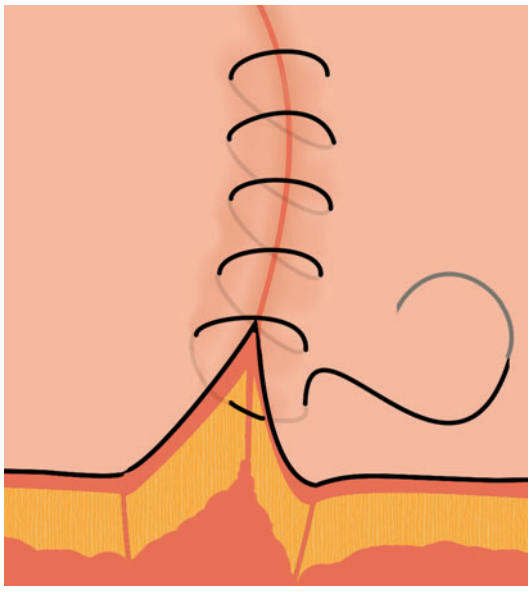

Fig. 8 Simple running closure. Symmetric "baseball stitches" are placed with a single suture and the ends are knotted. The width and depth of each bite should be equal

Two-Layer Closure

High-tension wounds and those with significant dead space require intradermal sutures to approximate underlying tissue. A simple interrupted stitch can then approximate this skin surface under lower tension (Fig. 12).

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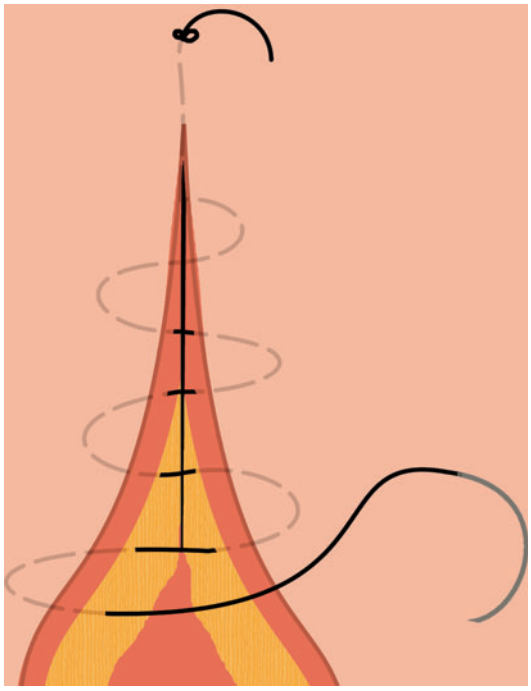

Fig. 9 Intradermal running closure. The wound is entered and exited through its apices. Horizontal "zig-zagging" passes are made with symmetric bites at the dermal-epidermal junction

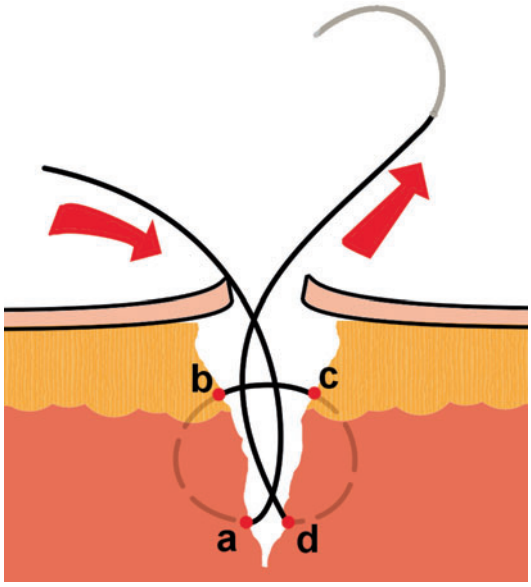

Fig. 10 Deep suture with buried knot. The suture enters the wound edge deep and, following the curve of the needle, exits superficially (still below the dermal-epidermal junction). This throw is reversed on the opposite wound edge and tied off, leaving a "buried" knot

Horizontal Mattress Suture

This suture technique should be considered for closure of gaping or high-tension wounds where intradermal sutures cannot be placed (such as palms or soles) because it spreads tension across the skin surface (Fig. 13). For this reason, horizontal mattress sutures are useful in areas with fragile skin [6].

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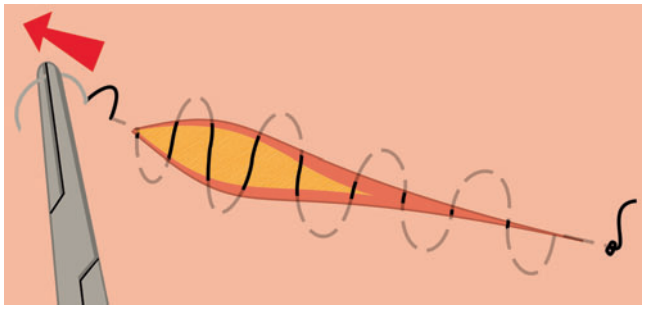

Fig. 11 Completion of intradermal closure. The needle exits the skin approximately 1 cm from the apex and the tail secured by adhesive strip

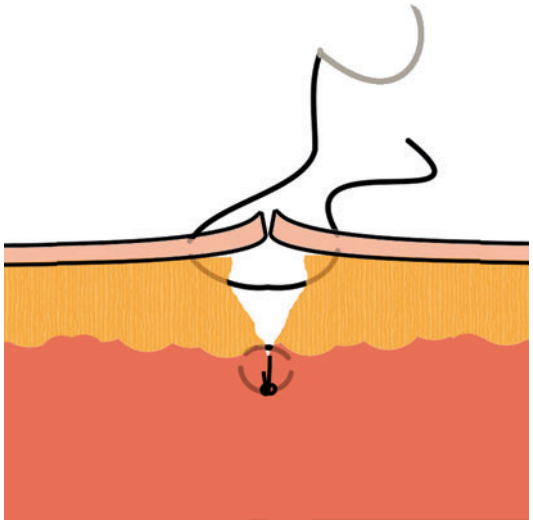

Fig. 12 Two-layer closure. A buried suture placed deep to a simple interrupted stitch. Note the area of undermining just below the epidermis

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 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.

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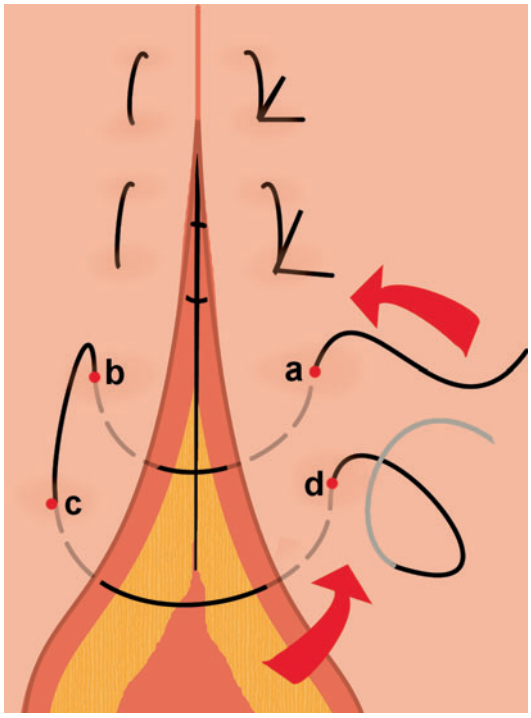

Fig. 13 Horizontal mattress sutu.re. The needle enters 0.5–1 cm from the wound edge, passes deep into the wound and exits symmetrically at the opposite side. The needle reenters and is passed in parallel to the first suture and exits the skin. The knot is then tied in parallel with the wound

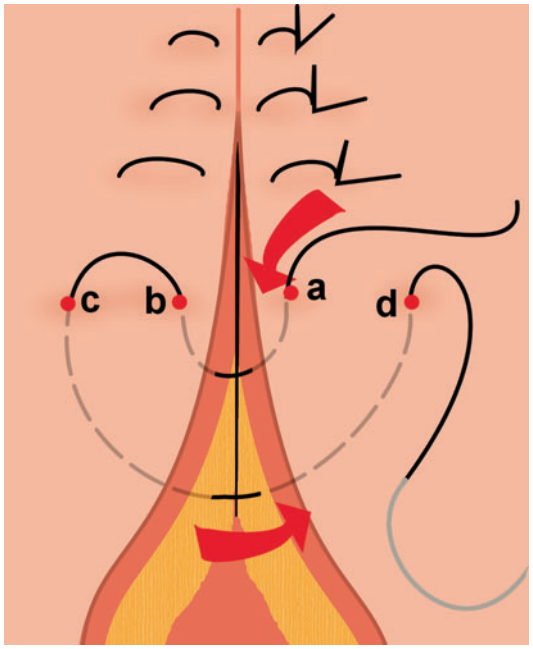

Fig. 14 Vertical mattress suture. The needle enters 0.5–1 cm from the wound edge, passes shallow and exits symmetrically at the opposite side. The needle then reenters laterally on the same side, enters deep into the wound under the previous suture and exits directly lateral to the initial entrance site. The knot is tied perpendicularly with the wound

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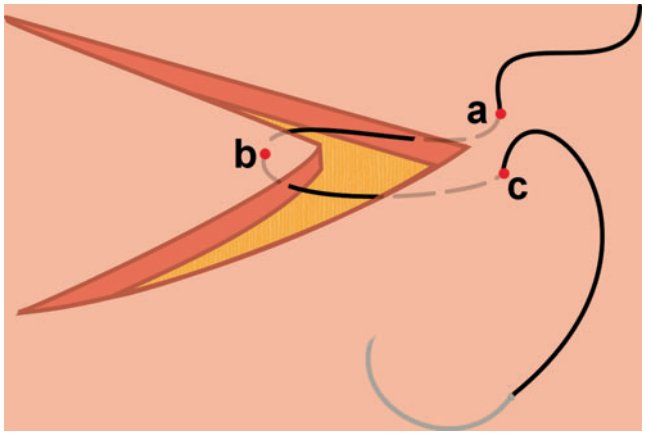

Fig. 15 V-flap repair

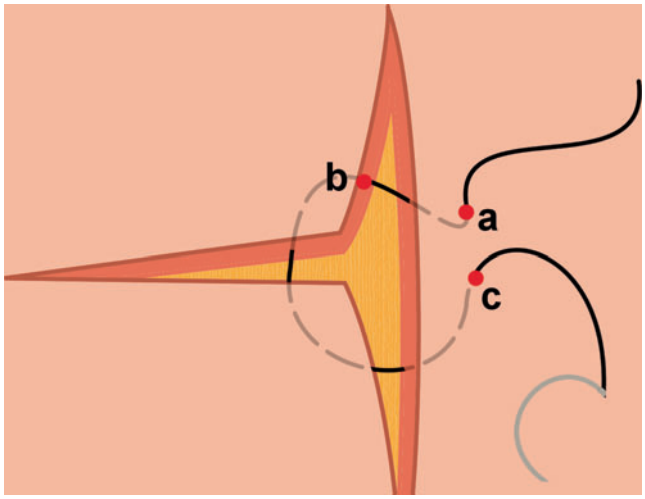

Fig. 16 T-laceration repair

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 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

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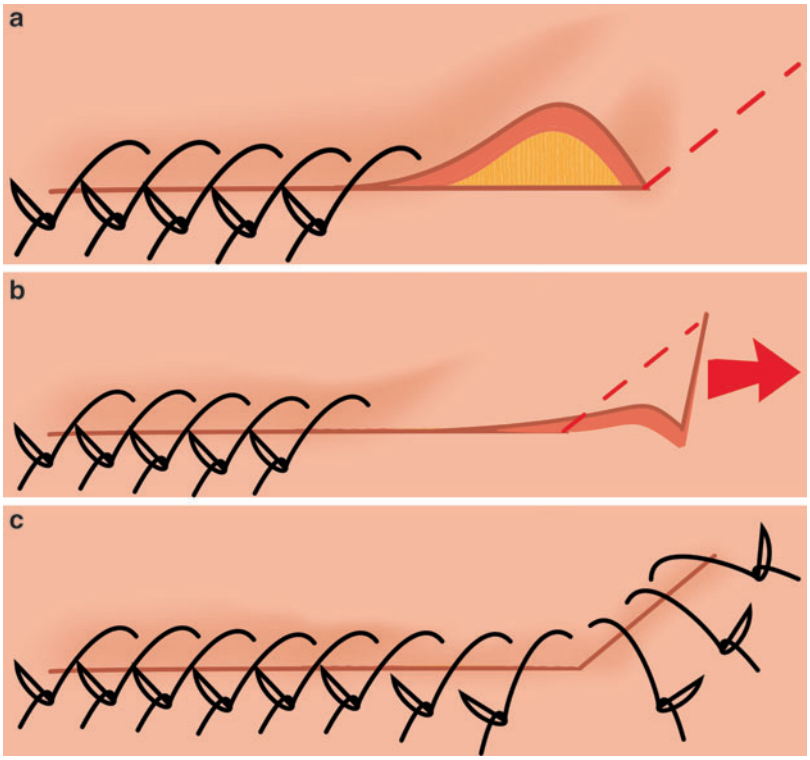

Fig. 17 Dog-ear repair 1–3. (**a**) Incise along the bulging dog ear to free the skin. (**b**) Pull freed skin edge and excise excess skin. (**c**) Close the new incision to allow skin to lie evenly

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.
- 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

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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 areas that are relatively hairless and will not become wet. Other applications are unsuitable.

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 4).

Wound Care and Follow-Up

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.

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Table 4 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

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 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 ("cleaning the skin until normal tissue is viewed") 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 5):

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Table 5 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

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Contents

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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 leading cause of death in the USA by the Centers for Disease Control (CDC) [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), 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

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Table 1 Causes of injury deaths in the USA in 2011 [1]

2011 injury deaths, USA	
All injury/accidents	187,464
Poisoning	46,047
Motor vehicle traffic	33,783
Firearm	32,351
Fall	28,360
Suffocation	16,832
Drowning	4,245
Fire/hot object or substance	3,172
Cut/pierce	2,587
Natural/environmental	2,193
Other	17,894

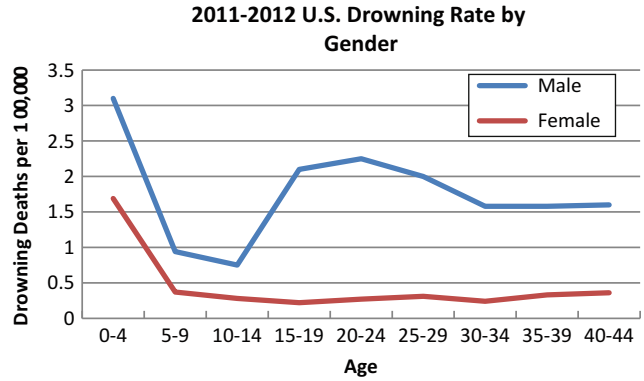

Fig. 1 US drowning death rates by age and gender, 2011–2012 [4]

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]. 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 secondary cardiac arrest and death if the drowning process is not arrested. 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 [3]. 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: 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 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. 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 [5]. 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 [5]. 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, so patents 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 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 and children should be supervised by an adult that is within arm's reach [6]. 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. Safety around the water should be taught at a young age, and swimming lessons are encouraged when age appropriate, usually around 4 years old according to the American Academy of Pediatrics (AAP) [7]. 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 [8]. 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 [8].

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 [8].

The middle ear is susceptible to both increased and decreased pressure, and "ear squeeze" is the most common form of barotrauma seen in divers [9]. 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 [9]. 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 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. 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. Do a full abdominal exam, especially in patients with a history of abdominal surgeries.

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 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.

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 [10]. 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 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 patent 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 [10]. 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 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 [11]. 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 now 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 often further subdivided into superficial and deep partial-thickness burns. However, in this author's opinion and experience, subdividing partial-thickness burns is pedantic, and burn specialists 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 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.

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 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.

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. The burn areas need to be exposed and the full extent of the burn 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. 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, 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. The easier – and this author's preferred – 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 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.

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 [12]. 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 [13]. Topical silver sulfadiazine (SSD, Silvadene) has historically

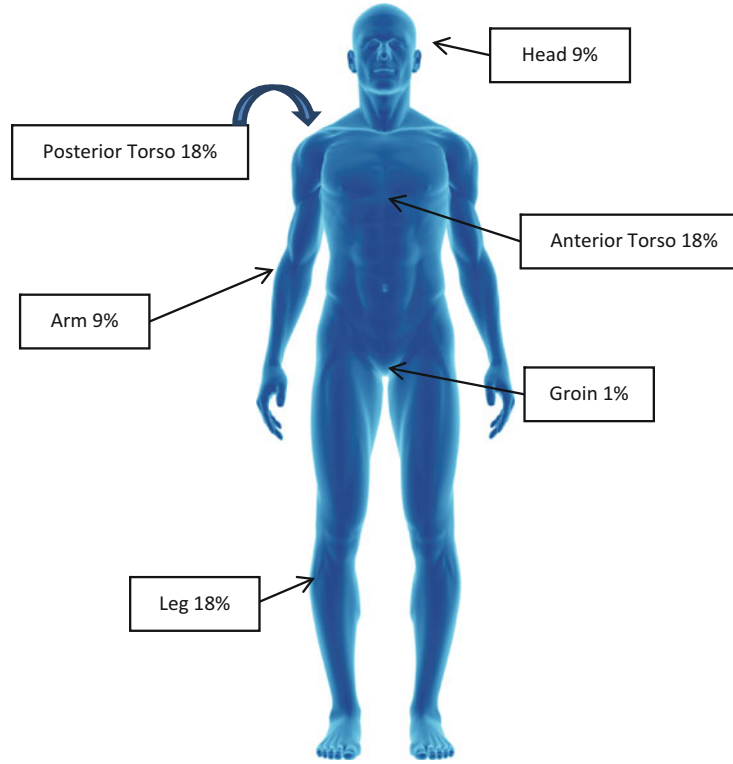

Fig. 2 Rule of nines to estimate %TBSA of partial- and full-thickness burns (Image created with adaptation of Microsoft Office© clip art)

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 [14]. 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 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 [14].

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 [15]. 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 [16]. The best marker of adequate

fluid resuscitation is urine output with a goal of at least 0.5 ml/kg/h.

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 [12].

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 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 [17]. 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 [18]. 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 [19].

Approach to the Patient

Diagnosis

History

Foreign body ingestion should be ruled out when evaluating a child with sudden onset of vomiting 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 [18]. 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 [20]. Contrast studies such as a barium swallow are not

Table 2 Endoscopic management of ingested foreign bodies (Source: adapted from Ikenberry et al. [21])

Endoscopic management of ingested foreign bodies
Emergent
Airway involvement
Esophageal obstruction
Esophageal battery or sharp object
Urgent
Blunt objects in the esophagus
Incomplete esophageal obstruction
Sharp foreign bodies in the stomach or duodenum
Magnets
Nonurgent
Coin in the esophagus >24 h
Objects in the stomach >2.5 cm
Batteries in the stomach >48 h

recommended due to the risk of perforation, the risk of aspiration, and the potential to make endoscopy more challenging [21]. 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 attempted. 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 [18]. 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 [18]. 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 should be observed as inpatients for obstruction as endoscopic removal is contraindicated for fear of rupturing the package and causing an overdose [17].

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 [22]. 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 four proposed techniques for removal, each with their own risks. 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

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

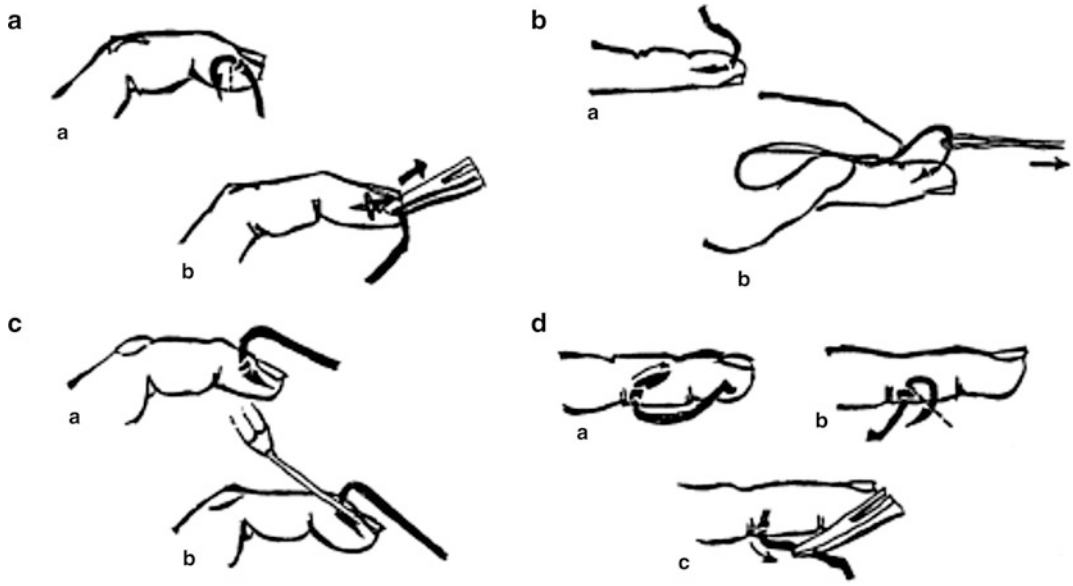

Fig. 4 Fishhook removal. (**a**) Simple retrograde pull. (**b**) String-yank technique. (**c**) Needle-cover technique. (**d**) Push and cut technique (Source: David et al. [24]. With kind permission of Springer Science and Business Media)

anesthesia. Chlorhexidine or iodine-based scrubs around the entry point are reasonable choices to clean the area prior to the procedure [23]. 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, should be given prophylactically to all deep wounds [22].

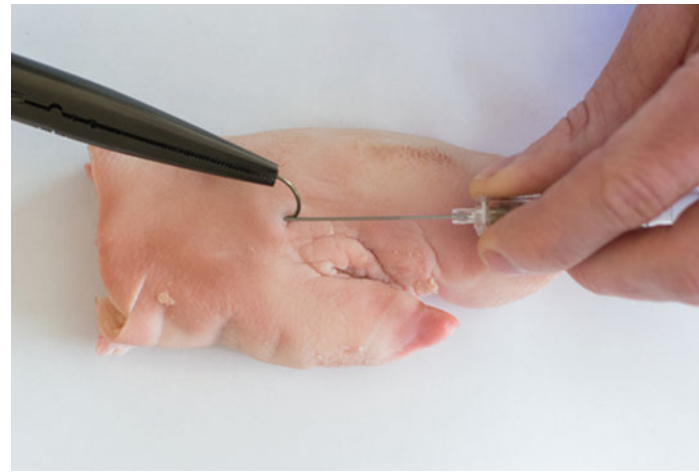

Fig. 5 Needle-cover technique. Note the hook is grasped with pliers and the needle enters at same location as the hook. This is an 18 gauge needle. No pigs were harmed in the making of this image

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 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 [22]. This is the only technique likely to work when dealing with a hook that has multiple barbs along its shaft. In this situation, the hook is advanced and the end opposite the barb is cut close to the skin, and the hook is advanced all the way through the skin without attempting to

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

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.

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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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. As such 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 in some detail 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 and the special populations of women, pediatrics, and geriatrics.

Physical Activity Guidelines

Regular exercise has been shown to decrease the risk of many chronic diseases as well as improve control of the same. 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 most recent guidelines in regard to physical activity are from the Department of Health and Human Services (HHS) who reviewed national and international data relating to physical activity and health and published the 2008 Physical Activity Guidelines for Americans. In it they recommend the average adult engage in at least 150 minute a week of moderate-intensity (brisk walking) or 75 minute a week of vigorous-intensity (light jogging) exercise. This should occur in 10 minute increments and preferably spread over the course of the week [1]. They also encourage muscle strengthening of all major muscle groups two times per week [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 ventricular mass, increased left ventricular wall thickness, and increase in left ventricular end-diastolic volume [2, 3]. Over the last decade, 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 heart rate [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. This is still a relatively new area in research, but it is thought that the sequelae of exercise – dehydration, lactate production, and hypoxia – impair blood viscosity during actual episodes of exercise, ultimately resulting in a decrease of whole blood viscosity in the resting athlete and supporting 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.

Chronic Disease

Medical Problems

Asthma

This common medical condition affects an estimated 8 % of the American population [5]. 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 constriction during activity and secondary airway hyperresponsiveness is more appropriately classified as exercise-induced bronchospasm (EIB). The mainstay of therapy includes inhaled beta-agonist, inhaled steroids, and masts cells 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, and provide an asthma action plan (AAP) and rescue inhalers for all asthmatics for practices and games.

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 a 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 [6].

Breathlessness, cough, wheeze, chest tightness, and excessive mucus production within the first 5–15 minute of exercise with resolution 1 h following cessation of activity are consistent with

EIB. However, these symptoms cannot solely be relied upon for definitive diagnosis; additional pulmonary testing and clinical examination are necessary. Spirometry may be used to assess these patients, but there are a few inherent characteristics of athletes that can make this difficult. Notably, forced expiratory volume (FEV) may be increased above the normal range in more 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 postexercise (known as an 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. Dry gas containing carbon dioxide, oxygen, and nitrogen is inhaled at a rate of 85 % maximum voluntary ventilation. FEV1 measurements are made and a decline of $\geq$ 20 % indicates EIB [7].

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 secondary to the inhalation of cold, dry air [6]. Swimmers have exhibited incidence of EIB six times greater than nonathletes and spring/summertime athletes, likely as a result of the chlorine exposure [8].

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 while exercising being asymptomatic at rest [9].

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. Recommend an indoor sport when possible. For winter athletes, breathing through a scarf can help. Educate the patient on proper warm-up including 15 minute moderate warm-up period followed by a 15 minute rest period which can induce a refractory period. Pharmacologic intervention should be considered with failure of conservative measures. First line is use of a short-acting beta-agonist 15 minute prior to exercise. Daily inhaled corticosteroids (ICS), leukotriene antagonists, or mast cell-stabilizing agents are second line [9, 10]. Long-acting beta-agonists are not as effective and should be used only in conjunction with ICS [11]. Education on use of medications for reversal of EIA when an exacerbation occurs with short-acting beta-agonists continues to be the standard of care.

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. Although many patients remain asymptomatic with a benign natural history, sudden cardiac 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. Despite being a relatively common inherited cardiac disorder, this condition can be hard to differentiate from the enlargement of the heart that can occur with elite athletes. As such, differentiating between HCM and physiologic nonpathologic left ventricular (LV) hypertrophy associated with extensive training ("athlete's heart") can be difficult. Distinction

of this disease has important implications since identification of cardiovascular diseases associated with sudden death may be the basis for 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. Major risk factors include prior cardiac arrest, unexplained syncope, a family history of SCD, left ventricular wall thickness $\geq$30 mm, an abnormal BP response to exercise (at high exertion peripheral pulses withdraw and systolic blood pressure decreases), and history of nonsustained spontaneous ventricular tachycardia [12]. 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?

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 [13]. 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. In office EKG should be considered for those athletes suspect of cardiac dysfunction. Advanced imaging of cardiac function by echocardiogram is the convention 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" [14]. 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 30 million people in America. It has been well established that regular physical activity can help decrease the risk of developing diabetes as well as serve to improve glycemic control.

The Diabetes Prevention Program, a large randomized controlled trial focusing on type 2 diabetes treatment through lifestyle modification, found that interventions producing weight loss through improved dietary intake and physical activity decreased the risk of diabetes by 58 % [15, 16]. Their recommendation for exercise modeled that of the Department of Health and Humans Services of 150 minute of physical activity a week consisting of brisk walking distributed over three separate sessions with at least 10 minute per session [15, 16]. 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 the type 1 diabetic, there are three considerations when participating in athletics. First, as previously mentioned, 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 diabetic 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 [17, 18].

Several recommendations can be made to type 1 diabetics to avoid these complications. Adjustments to carbohydrate intake rather than insulin dosing are associated with fewer exercise-related complications [17, 18]. Athletes should check their blood sugar prior to exercise and supplement with a high-carbohydrate snack if less than 150 prior to exercise [18]. For endurance athletes, training sessions longer than 1 h should consider carbohydrate supplementation [17, 18]. All athletes should have a postexercise snack in order to combat the delayed hypoglycemia risk as well as frequent blood sugar checks every few hours in that postexercise period [17].

The insulin pump is becoming a more 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.

Hematological Disease

Anemia

As discussed above, in exercise physiology, the blood and its ability to transport oxygen are an important part of an athlete's performance ability. There is a phenomenon known as "sports anemia" most common in endurance athletes. This refers to the dilutional pseudoanemia that results from plasma expansion. Repetitive long workouts resulting in a hemoconcentration from dehydration result in an overshoot of plasma expansion postexercise and ultimately up to 1.5 g/dL below normal Hgb levels [19]. This should not be high on the differential for nonendurance athletes, but the diagnosis can be tested by stopping workouts. The athlete's Hgb should normalize within 5 days [19]. It is an adaptive response and ultimately does not need to be corrected.

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. It can occur in up to 20 % of menstruating females and 6 % and 4 % of postmenopausal women and male athletes, respectively [19]. Etiology includes the same as those in the general population – GI bleeding, NSAID use, and menstruation in females. Other 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 [19]. Iron deficiency anemia should be worked up and treated similarly to iron deficiency anemia in the general population (chapter ?).

In athletes there does appear to be an increase in nonanemic iron deficiency. When ferritin, a predictor of iron stores, is used as an indicator for anemia in studies, there is consistently a difference of anemia in athletes, especially endurance athletes [20]. The utility of replacing iron in these athletes is controversial. A recent review of 17 studies argued that iron supplementation to achieve normal ferritin levels did statistically improve aerobic capacity [20]. Given the controversial nature of this therapy, athletes thought to fall into this category should be referred to a sports specialist for evaluation and management.

Macrocytic and hemolytic anemia 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 results in endurance athletes from repetitive heel strike, muscle use, or cardiac valve turbulence [21]. It rarely requires treatment.

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. Under normal physiological conditions, this is typically benign and easily controlled. However, in the athletic population, heat, high altitude, and intense training can put these individuals at increased risks of medical complications such as splenic infarction, hematuria, exertional rhabdomyolysis, and sudden death.

In 2010–2011 the NCAA started to require all Division 1 athletes know their sickle cell status or sign a waiver, thus bringing sickle cell trait to the forefront of several considerations during a pre-participation physical. There is much discussion as to whether this screening should expand outside Division 1 and whether it should be targeted at specific high-risk sports (football and basketball) and populations (African, Mediterranean, and Middle Eastern) [22]. Regardless, athletes with known sickle cell trait should be made aware of the risks. Appropriate precautions should be taken. The athlete should be conscientious of staying well hydrated and tapering workouts to not overexert themselves, especially in hot and high-altitude conditions.

Bleeding Disorders

Von Willebrand's disease, hemophilias, and immune thrombocytopenia are common bleeding disorders that are often discovered in childhood; thus, they can present in the young athlete. The etiology, prevalence, work-up, and management do not vary significantly from the general population. However, once diagnosed, appropriate modifications need to be made in the athletic population. Type of exercise and sport should be tailored to the athlete's interest. Swimming, bicycling, skating, and weight training are good sports to recommend. Avoidance of contact sports should be emphasized along with the use of protective equipment. These diseases do not preclude someone from participation, but it is important to ensure appropriate education is done with the patient.

Skin

Tinea Corporis Gladiatorum

Tinea corporis gladiatorum (TC) is a fungal rash caused by *Trichophyton tonsurans* most often seen in contact sports, especially wrestling. Studies have estimated it to be prevalent anywhere from 24 % to 77 % of individuals in wrestling [23]. 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.

Treatment can be either topical or oral. Topical application of clotrimazole twice daily or oral fluconazole 200 mg weekly is a recommended treatment. One small study suggested that application of oral antifungals weekly has resolution of positive cultures 1 week earlier than topical [23]. The most important aspect of treatment, however, is prevention. It is recommended to keep these athletes out of practice for 2 weeks of treatment. Discourage sharing of equipment among the athletes and encourage frequent cleaning of personal equipment.

Tinea Pedis

Another common fungal infection among all athletes is tinea pedis caused by *T. rubrum* and *T. mentagrophytes*. Walking barefoot on communal floors, wearing occlusive footwear, sweating excessively, and poor circulation can all predispose these athletes to this infection. Similarly to tinea corporis, the diagnosis can be made clinically or by KOH prep.

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 with these bacteria. Well-defined, erythematous, yellow, crusted plaques are characteristic of presentation.

Folliculitis occurs when these bacteria infect the athlete's follicles. The hair follicles become red and inflamed and can have pustule drainage. The rash tends to be itchy and if deeper also painful.

Mupirocin can be used, but with extensive rash, treatment with penicillin or cephalosporin is recommended for a week [23]. The athlete should be kept out of their contact sport for 5 days [23]. 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 [23].

Nail Dystrophies

Trauma and pressure to the nail plate and periungual area can result in sport-specific changes that often look similar to onychomycosis so it is important to be aware of these nail dystrophies.

Runners develop jogger's toe from repetitive thrusting of the toe into the shoe that result in a subungual hematoma. Furthermore, 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 indicate fungal infection or melanoma. However, occasionally the patient is having too much pain from these nail changes to effectively participate. In these instances, if there is a clear subungual hematoma, then treatment by drilling a hole through the nail bed is advised [23]. If there is no clear hematoma, but there is evidence of nail bed changes, completely removing the nail is a reasonable treatment option [23].

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 [23]. Mogul's palm occurs on the hands of skiers from repetitive pole planting. They often can be confused with melanoma. If there is suspicion for melanoma, a biopsy should be done; otherwise paring down the lesion with a surgical blade can remove the old hemorrhage [23].

Special Populations

For a family physician, the patient population ranges across all age groups and both genders. 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 [24]. In the past 10 years, a few studies have shown regular exercise to decrease prolactin and progesterone resulting in a decrease in fatigue and improved concentration as well as improvement of premenstrual symptoms of low back pain, pelvic pain, anxiety, and depression [25, 29].

On the other side, as female participation in sports has increased, a set of health problems unique 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. A recent meta-analysis suggested that the prevalence of all three components among female athletes was small (1–15.9 %); however, the prevalence of one or two components ranges from 16 % to 60 % and 2.7 % to 27 %, respectively [26]. 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 [27]. This low energy availability coupled with the physical and mental stress of training can lead to menstrual irregularity [27]. Finally, this low energy state results in the decrease in insulin growth factor and hypoestrogen leading to low bone mineral density [27].

Currently, there is no ideal screening tool for the female athlete triad, but if an athlete is found to have one component, it is important to screen for the other two. 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 [27, 28]. Other treatments can include pharmacological therapies such as SSRIs and hormone replacement but 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. A meta-analysis of recent studies looking at exercise in pregnancy outlines the many benefits of staying physically active during pregnancy and include [30, 31]:

1. Lower risk of gestational diabetes
2. Enhanced sleep
3. Reduced bone density loss
4. Reduced physical discomfort
5. Maintenance of appropriate weight
6. Improved mental health
7. Lower birth weights despite increased gestational ages
8. Higher apgar scores

The recommendations from the 2009 American College of Obstetricians and Gynecologists in regard to exercise during pregnancy are as follows [31]:

1. Achieve regular moderate exercise at 30 minute or more most days of the week.
2. Avoid exercises requiring the supine position after 12 weeks gestation due to increase 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.

They also note in these recommendations that there are no reports of hyperthermia being associated with teratogenicity although avoiding extreme overheating is recommended. Additionally, there is no published evidence on the effects of strenuous training, so these athletes should be monitored closely [31].

In summary, women who were previously healthy prior to pregnancy can continue with their training programs during pregnancy. They can restart their training programs when they feel ready, some as early as 1 week [31]. Women with significant cardiac or respiratory disease or complications to the pregnancy should be monitored carefully during exercise [31].

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 very old being those over age

85 [32]. 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. In addition, the elderly specifically experience the benefits of better balance and improved cognition allowing them to maintain independence [32]. However, it is important 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 [33]. 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 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 [24, 33].

In order to maximize the benefits of exercise and limit the risks of adverse outcomes, the American College of Sports Medicine along with the American Heart Association has set forth the following recommendations for physical activity [34]:

1. Minimum of 150 minute of moderate intensity or 60 minute of vigorous physical activity per week
2. No more than 10 % increase in volume or intensity at a given session
3. Resistance training with 10–15 repetitions of 8–10 exercises that train major muscle groups twice per week
4. Flexibility exercises 10 minute twice a week with 10–30 s of 3–4 repetitions per static stretch
5. Balance activities twice per week

Pediatrics

In 2012 the CDC estimated that 18 % of children 6–11 years old and 21 % of adolescents aged 12–19 fit into the obese category. As such it has become a public health concern to encourage children and adolescents to participate in physical activity in a healthy and beneficial way. On the other hand, there has been a significant increase of participation in team sports in this population. As a family physician, 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.

For the average patient in this population, the Physical Activity Guidelines for Americans set for the following recommendations in 2012:

1. Participate in 60 minute or more of moderate to vigorous intensity aerobic physical activity daily.
2. Resistance training on three nonconsecutive days. This can be part of the 60 minute of daily activity and includes activities such as tug-of-war, rope climbing, or push-ups.

The benefits of following these recommendations include healthy body composition, increased development of bone mass, improved self-esteem, and decrease in anxiety and depression [35].

Several medical conditions such as asthma, exercise-induced asthma, hypertrophic cardiomyopathy and sudden death, type 1 diabetes, and sickle cell anemia are often more prevalent in the pediatric population and have been addressed previously.

Hypertension in the pediatric population is defined by a blood pressure that is >5 mmHg above the 99th percentile for age, gender, and height. These athletes should avoid power lifting and body building until successfully treated [36].

Mononucleosis is a common virus in the adolescent population. One of the sequelae of this virus is an enlarged spleen. Children known to be affected with mononucleosis and having an acutely enlarged spleen should be kept from contact sports until resolution of the enlarged spleen [36]. According to the AMSSM consensus

on mononucleosis and athletic participation, players can return to sport 3 weeks from day of diagnosis [37].

Congenital abnormalities also become a consideration in this population. For example, athletes with Down syndrome or juvenile rheumatoid arthritis need to be assessed for atlantoaxial instability and likely should be kept from certain contact sports such as football, basketball, and wrestling [36]. Athletes with cystic fibrosis should be assessed for the functional capabilities and cleared for sports based on these considerations [36].

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Athletic Injuries

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Musculoskeletal concerns account for up to 30 % of patient encounters within family medicine. Youth sport participation continues to increase nationwide with over 30 million youth and teens participating [1]. High school athletics alone accounts for over two million injuries, half a million physician visits, and 30,000 hospitalizations annually [2]. Growing sports specializations within adolescents has led to an increase in overuse injuries; accounting for half of all adolescent injuries [1]. Adults are not immune to athletic injuries, as weekend warriors suffer numerous injuries. Weekend warriors commonly suffer ankle injuries, knee injuries, dislocations, and overuse injuries in attempts to stay active.

Injuries result after an insult to bone or soft tissue structure (muscle, ligament, or tendon) and produce disruption in the normal anatomy. Acute injuries are usually secondary to some form of trauma while chronic injuries are usually the result of overuse with or without associated biomechanical deficiencies. Prior injuries to a joint that did not undergo appropriate rehabilitation can also lead to increased risk to further injury. A majority of sports-related injuries occur to the axial skeleton; however, mild traumatic injuries to the brain, i.e., concussions, are becoming a growing concern within our society with over 300,000 sports-related concussions occurring annually [3]. 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, pain control, and stabilization of surrounding tissues to prevent additional injury to the area. Inflammation can be reduced with rest, ice, compression, and elevation (RICE). Nonsteroidal anti-inflammatory drugs (NSAIDs) can also be of use in the reduction of inflammation and pain control. Pain control can be accomplished with immobilization, NSAIDs, acetaminophen, muscle relaxants, or opioids. Opioids should be reserved for dislocation and fracture pain control. Imaging of the injured area is usually required in order to fully assess the injury.

Imaging modalities include x-rays, computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound (US). Imaging will alert the provider 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. Unfortunately, some injuries are not to be managed conservatively as discussed above. Referral to a sports medicine physician or orthopedic surgeon is sometimes required for more definitive treatment.

General Fracture Management

A large percentage of nonoperative fractures can be managed by family physicians. Understanding the patient's entire medical picture allows the provider to identify risk factors for impaired fracture healing. Physical examination on 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 on 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 bone scans, CT, or MRI could be warranted. All fractures should be assessed for closed/open status, displacement, angulation, direction of fracture line, and presence of multiple fracture segments in order to provide appropriate care.

The healing of fractures occurs over a several-month period; understanding this process is necessary to appropriately treat fractures. The initial inflammatory phase occurs almost immediately after injury through recruitment of inflammatory cells and formation of a hematoma. Osteoblastic cells are recruited and responsible for the initial remodeling of the injury site. Within the first 2–3 weeks, a soft callous is formed, signifying the arrival of osteoclastic cells. By week 6–8 post injury, a hard callus replaces the soft callus, signifying clinical union. Final bone strength and radiographic resolution occur 3–6 months after injury. Multiple factors can inhibit the above healing process. Smoking, diabetes, and chronic oral steroid usage are common problems managed by primary care providers that inhibit bone healing. NSAID usage, especially during the first 2–3 weeks of healing, can inhibit 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 and opioids if needed.

Immobilization via splinting or casting throughout healing is critical. Any fracture that has significant displacement or angulation requires reduction prior to immobilization. Post reduction 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 fracture is high but radiographs are negative, immobilize as if a fracture is visualized and reevaluate the patient in 1–2 weeks with additional imaging. Splinting should always occur for the first 3–5 days after initial injury. Circumferential casting can be applied after this time period for a more permanent immobilization solution. Casting a patient during the acute inflammation 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* [4] and *Handbook of Fractures* [5] are both excellent resources for primary care providers who provide fracture care.

Concussion

History

Concussions result from either direct trauma or application to indirect forces to the face, head, or neck. Patients can complain about a diverse group of symptoms: headaches, balance disturbances, retrograde amnesia, nausea, photophobia, phonophobia, visual tracking issues, slowed

cognition, mood changes, sleep disorders, concentration issues, confusion, and dizziness. Although once thought to be required for diagnosis, loss of consciousness can occur but is not required. Symptoms classically begin immediately after the injury, but delayed presentation of symptoms for up to 72 h can occur. Most individuals will have resolution of symptoms within 10 days; however pediatric and adolescent patients may have prolonged symptoms [6, 7].

Physical Exam

Sideline evaluation of patient should include complete neurological examination and cognitive evaluation. The SCAT3 and Child SCAT3 assessment tools [8, 9] are free resources to assist in initial and follow-up evaluation of concussed individuals. In the acute setting, it is important to evaluate for associated cervical spine injuries. Acute changes in neurologic status, personality changes, or acute worsening of headache should signify the need for additional evaluation at higher levels of care such as the emergency room. Follow-up evaluations should focus on patient's cognitive status, balance testing, and neurological evaluation (reflex testing, rapid alternating eye movements, visual tracking, etc.).

Imaging

Routine imaging after a concussion is no longer indicated. If initial evaluation findings are concerning for an intracranial bleed, a CT scan is indicated [6, 7]. Imaging of the cervical spine is indicated if associated injury is suspected.

Management

Acute management of concussed patients involves immediate removal from competition and close monitoring. Concussed athletes should be reevaluated throughout the rest of the game and afterwards. Suspected concussed athletes should never be allowed to return to competition the day of injury [6–8]. Concussion grading is no longer used and should not be applied to management decisions. The current hallmark of the management is physical and cognitive rest until symptom resolution. Cognitive rest includes removal from classroom activities if needed. A transition process back to full academic participation including extended deadlines on assignment, extended test taking time, and transition from active listener to active learner in the classroom should be utilized [10]. Most sport medicine providers employ a graded return to play physical activity/sports once the patient is symptom free [6, 7]. Computer-based cognitive testing can be used as an adjunct in helping determine when a patient has returned to his or her baseline. Some school districts now obtain baseline neurocognitive testing in the contact sport athletes to help in this, but current evidence is conflicting on the reliability of baseline testing [11].

Symptomatic care for headaches should not include NSAIDs for the first 48 h after injury. Physical therapy for concurrent neck soft tissue injuries can help alleviate tension-type headaches. A patient with prolonged symptoms should be treated with a multidisciplinary approach (pharmacologic, speech therapy, vestibular rehabilitation, physical therapy, and optometry/ophthalmology) [12]. In patients with prolonged symptom, light aerobic exercise should be encouraged as long as it does not worsen their current symptoms [12].

Acute Back Pain

History

Acute low back pain is defined as pain that has been occurring for less than 3 months time. The most important tool in its evaluation is a thorough history and physical. History should focus on associated red flag symptoms such as trauma, fever, chills, new onset or worsening bowel or bladder incontinence, saddle anesthesia, age greater than 50, and new motor or sensory deficits [13]. Movements that worsen symptoms such as hyperextension should be noted in youth athletes,

especially weight lifters, cheerleaders, and gymnasts.

Physical Examination

A standard musculoskeletal exam evaluating range of motion, areas of tenderness to palpation, hamstring and hip flexor flexibility, and lower extremity nerve root examination should be completed. The location of tenderness on palpation will assist the provider in determining if 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. Special tests are often used to evaluate for sciatica and possible spondylolysis. The straight leg raise is often used to evaluate for radicular symptoms (sciatica). While the straight leg raise does have high sensitivity, it exhibits poor specificity. Palpable step offs, loss of normal lumbar spine lordosis, tight hamstrings, pain with single leg lumbar extension, and vertical position of the patient's sacrum are diagnostic clues in identifying acute spondylolysis [14].

Imaging

In the absence of any red flag findings, no imaging is indicated. If other signs or symptoms of fracture are present, then x-ray is the initial imaging of choice.

Treatment

Patient education is the foundation of treatment of acute low back pain. Often, no definitive cause is identified; education on the natural course of acute low back pain and encouragement of continued physical activity should occur [15]. Conservative treatments with NSAIDs or acetaminophen are options for pain control. If muscle spasms are appreciated on examination, a short course of muscle relaxants should help symptoms; however, the patient should be advised of muscle relaxant's side effect profile and dosing precautions prior to initiating therapy. Opioids should be reserved for severe pain that has not responded to more conservative treatment options. Failure of pain control with opioids should cause a reevaluation of possible causes of the patient's symptoms. Home exercises, osteopathic manipulation therapy, and formal physical therapy are additional management options [13, 15].

Rotator Cuff Injuries

History

Patients will often present with nocturnal pain occurring when lying on the affected shoulder. Accompanying pain and/or weakness when raising the arm over shoulder-height is also characteristic. While some rotator cuff injuries occur from an acute injury, most result from cumulative microtrauma.

Physical Exam

Inspection can reveal scapular dyskinesia and/or muscle atrophy of the supraspinatus or infraspinatus. Palpation of the lateral shoulder over the subdeltoid bursa and rotator cuff insertions can elicit pain. Active range of motion will be decreased compared to passive range of motion. Special tests have been developed to test specific rotator cuff muscles. Jobe's "Empty Can" Test evaluates the supraspinatus integrity. 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 [16, 17].

Imaging

Radiographs consisting of three views of the shoulder (AP, axillary, and scapular Y) should be obtained. These views 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" is suspicious for a rotator cuff tear. If a detailed evaluation of rotator cuff anatomy is desired, a MRI should be considered.

Management

Acute full-thickness rotator cuff tears should be referred to an orthopedic for surgical management. Physical therapy is the cornerstone of conservative management. Rehabilitation exercises focus on restoring shoulder range of motion, correcting shoulder biomechanics through rotator cuff strengthening and scapular stabilization, and correcting poor static and dynamic posture [17]. NSAIDS and activity modification such as limiting overhead activities can complement the rehabilitation process. Cortisone 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 [18]. As with all musculoskeletal injections, emphasis should be placed on appropriate rehabilitation in conjunction with the injection.

Shoulder Instability

History

The term shoulder instability can be used to describe an acute dislocation or subluxation along with chronic instability leading to recurrent subluxations. 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 approximately 5 % of the time and are associated with electrocutions or seizures. Chronic shoulder instability can be the result of prior dislocations or nontraumatic repetitive microtrauma. This is often seen in athletes with repetitive overhead motions such as swimmers, baseball pitchers, and volleyball players. 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 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.

Physical Examination

Gross shoulder deformity will be present with both types of 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 so appropriate treatment options can be discussed with the patient. Joint laxity testing can be completed with any number of the following test: apprehension test, relocations test, sulcus sign, load and shift, and jerk test. Testing for associated labrum pathology should also be completed. Multiple examination techniques have been described and include dynamic sheer, passive distraction, biceps load, and O'Brien's [16, 17].

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 or bony Bankart lesion.

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 Hippocratic technique, Stimson technique, and scapular manipulation technique; Kocher's technique and Milch's technique are the two main leverage techniques. Stimson's method is a relatively nontraumatic technique that is easy to complete field side [19]. The patient should lie prone on an exam table or bench with the affected arm. Gentle downward traction is applied in order to facilitate the relaxation of muscles and spontaneous reduction [19]. 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 [16]. After reduction, the patient should then be immobilized in a sling for 2–4 weeks with early physical therapy. Positioning (internal rotation versus external rotation) of the arm during immobilization remains controversial [16, 19]. Surgical consultation for discussion of operative treatment options should be considered in a young athlete after his or her initial dislocation; risk of recurrent dislocation is approximately 90 % if initial event occurs prior to the age of 20 [16, 19].

Aggressive physical therapy with strengthening of the rotator cuff and scapular stabilizing muscle remains the mainstay to 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 mirrored those of unidirectional instability but can be discussed if the patient fails conservative management [16].

Biceps Tendon Rupture

History

Rupture can occur at three locations: long head origin within the labrum, short head origin on the acromion, and common distal insertion; the majority of ruptures occur at the insertion of the long head. The most common mechanism of injury involves the elbow being forcibly flexed against resistance. Tears can also occur after prolonged wear and tear to the tendon; most often, these patients will have an associated history of chronic shoulder pain and impingement on the affected side. With an acute rupture, the patient may describe an audible pop followed by gross deformity in the anterior arm with associated ecchymosis.

Physical Examination

With a proximal rupture, patients will be tender over the anterior shoulder along with associated swelling and ecchymosis. Flexing of the elbow will often show a "Popeye deformity" where the bicep will be more prominent over the middle of the humerus compared to the unaffected side. A small decrease in resisted elbow flexion and supination may be observed as well [17]. Distal bicep tendon rupture 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 films or elbow films should be ordered depending on the site of tendon rupture to

evaluate for any associated bone injury. Distal tendon injuries should be further evaluated with MRI. Given the long tendon's origin within the labrum, patients with proximal injuries and associated shoulder pain/instability should undergo MRI arthrogram of the shoulder to identity any associated labrum injuries.

Treatment

Proximal bicep ruptures should be referred to physical therapy. If an associated labrum injury is found and the patient does not respond to physical therapy, referral to an orthopedic surgeon should be made. Referral to orthopedics should not be delayed for distal biceps rupture as definitive treatment is surgical and significant morbidity can be seen with delayed operative management [20].

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 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 associated weakness with the above resisted testing should raise suspicion of an alternative diagnosis such as radial tunnel syndrome [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. 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, NSAIDs, steroid injections, and counter load braces have been the mainstay of conservative treatment [20, 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 [21]. New treatment techniques such as dry needling, prolotherapy, topical nitroglycerin patches, and platelet-rich plasma (PRP) are emerging as treatment options [21]. Recalcitrant cases (greater than 18 months of symptoms without response) can be referred to orthopedics for possible operative debridement [22].

Scaphoid Fracture

History

The most common mechanism of injury involves a fall onto an outstretched hand (FOOSH injury). Patients describe pain along the radial aspect of the wrist, usually within the anatomic snuffbox. Wrist pain can be worsened with radial and ulnar deviation and with gripping activities.

Physical Exam

Swelling may be present over the anatomic snuffbox. Pain is reproducible with palpation of the anatomic snuffbox. Wrist active range of motion can be fairly normal but pain is reproducible at the extremes of wrist range of motion, especially with radial and ulnar deviation. Loading of the thumb's carpometacarpal joint will also elicit pain. Watson's 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 four views of the wrist: clinched fist PA, scaphoid, lateral, and oblique views. The scaphoid view puts the wrist in ulnar deviation and allows better visualization of the proximal scaphoid. The clinched 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 disassociation on initial films, a comparison view of the contralateral wrist should be obtained for comparison.

Management

Management depends on location of the scaphoid fracture given the bone's tenuous retrograde blood supply. Indications for orthopedic referral include greater than 1 millimeter (mm) of displacement, fracture comminution, scapholunate angle greater than 60°, scapholunate disassociation, and greater than 10° of angulation [23]. Successful healing with nonoperative treatment occurs in 100 % of distal third and tuberosity fractures, 80–90 % of waist fractures, but only 60–70 % of proximal fractures [23]. Early consultation with orthopedic surgery should be strongly considered in proximal third fractures because of significant morbidity from malunion, nonunion, and/or avascular necrosis (AVN) [24].

If the decision is made to treat the patient nonoperatively, the exact type of cast (short arm thumb spica versus long arm thumb 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 fractures 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 to 12 weeks, while proximal fracture healing usually requires 12–24 weeks. Due to the prolonged immobilization times required for most scaphoid fractures, patients will likely benefit from formal physical or occupational therapy to expedite a safe return to work or sports [23–25].

Patients will often present after a FOOSH injury but their initial imaging will be negative. If a scaphoid fracture is suspected, the patient should be immobilized in a short arm thumb spica splint or cast for 2 weeks with repeat films in 2 weeks time. If follow-up plain films are still negative, additional imaging with CT or MRI is indicated if clinical suspicion for a scaphoid fracture remains. Due to prolonged immobilization time, patients will likely benefit from formal physical or occupational therapy to expedite a safe return to work or sports.

Mallet Finger

History

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 the patient is preparing to catch a ball.

Physical Exam

With the practitioner stabilizing the proximal interphalangeal (PIP) joint, 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. As with all finger injuries, the assessment of associated joint collateral ligaments, finger alignment, and possible rotational deformity should be assessed.

Imaging

A lateral x-ray view of the affected finger will identify bony avulsion and subluxation of DIP joint or be normal with a tendon avulsion injury.

Management

The majority of mallet finger injury can be managed conservatively. Indications for surgical referral include inability to adequately reduce the avulsed fragment, inability to obtain full passive extension of the DIP, and greater than 30 % of the articular surface of the DIP being involved [26, 27]. 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; a Cochrane Review concluded that no splint type was superior, but stressed the need for the splint to be robust enough for daily wear [28].

Jersey Finger

History

Forceful extension when trying to flex the DIP joint can be experienced by an athlete getting his or her finger caught in a jersey or when rock climbing. Seventy five percent of injuries involve the fourth digit.

Physical Exam

A patient will commonly present with pain along the palmar aspect of the DIP and the involved finger held in slight extension relative to the other. Although the patient may be able to weakly flex the DIP, it will be dramatically weaker than their unaffected fingers. It is imperative to isolate the DIP during testing to isolate the flexor digitorum profundus. Finger alignment and rotation should also be assessed [26].

Imaging

PA and lateral view radiographs of the involved finger can identify avulsed bony fragments or fractures.

Management

All jersey fingers require urgent referral to orthopedic surgery. Delay in referral can lead to flexor digitorum profundus retraction and subsequent surgical complications. The involved finger should be splinted in a flexor tendon splint and referred to an orthopedic surgeon as soon as possible [26].

Iliotibial Band Syndrome (ITBS)

History

ITBS is an overuse injury commonly seen in runners or cyclist. The patient can complain of pain anywhere along the IT band but most commonly will complain of lateral thigh or lateral knee pain. Proximal pain usually refers to over the greater trochanter of the hip, while distal pain localizes over the lateral femoral condyle or Gerdy's tubercle. The pain can usually be localized and reproduced with palpation. Often, the

patient has increased their training significantly in terms of mileage per week or intensity. Runners and bikers are especially prone to IT band problems due to the repetitive flexion and extension at the knee.

Physical Exam

Inspection of lower extremity anatomy can help determine if a person is predisposed to IT symptoms. Anterior pelvic tilt, genu varum, and excessive foot pronation leave the patient susceptible to chronic IT band irritation. Gait analysis may reveal a Trendelenburg gait – an indication of hip abductor weakness. Ober's test reveals IT band tightness, and the patient usually has a limitation of hip abduction. Additionally, these patients often have tight hamstrings [29].

Imaging

If pain is located distally, anterior-posterior, lateral, and sunrise radiographic views of the knee can reveal arthritic changes within the knee or patellar mal-alignment.

Management

Treatment of ITBS should focus on correcting underlying biomechanical causes of symptoms. Weakness in hip abductors, specifically gluteus medius, should be addressed; additionally, hip flexor, short hip external rotator, and hamstring flexibility and strength should be maximized. Excess foot pronation should be treated with shoe inserts. Appropriate weaning/breaking in of insoles should be discussed with patients. Activity modification including reduction in training mileage and/or intensity assists with initial symptom management. Changing training to a non-weight-bearing activity such as swimming or elliptical can help keep a patient motivated throughout their rehabilitation process while also curtailing the inflammatory process. Ice massage over Gerdy's tubercle and cross-frictional massage of the ITB are useful adjacent therapies. The patient will need to gradually return to activity as re-irritation of the IT band is very common. Once the patient is back to normal weight-bearing activities, it would be wise to incorporate a maintenance rehabilitation exercise program into their weekly workouts to prevent reoccurrence of symptoms [29].

Patella Dislocation

History

Significant pain and swelling are the most common complaints associated with patella dislocations. Common mechanisms of injuries include playing sports or dancing where repetitive knee valgus and lower leg internal rotation occur within a closed kinetic chain. Injuries may be from an acute event or from repetitive microtrauma. The dislocation resolves spontaneously with knee extension and the patients will often present post spontaneous reduction. History and complaint of recurrent sensation of patellar subluxation are the only 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 [30]. An obvious deformity will be seen if relocation has not occurred. If relocation has recurred, the medial retinaculum and lateral femoral condyle are often tender to palpation. A positive patellar apprehension test will be noted, and laxity in patella movement will also be observed.

Imaging

Standard three-view knee films should be obtained to assess for fractures. If the exam does not ensure intact knee ligaments, then an MRI may be needed to look for associated ligamentous

or meniscal injury. MRI is indicated after an acute injury with significant hemarthrosis.

Management

In the event that the patella has not been relocated, reduction should be completed. 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 for 3–6 weeks should occur after reduction. Controversy exists on surgical versus conservative management on primary traumatic patellar dislocation. Recent research does not show benefit to operative management after an initial traumatic injury. 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 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. Patients with recurrent dislocations should be evaluated by an orthopedist [30].

Knee Ligament Sprain/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 (CJSM article); its main function is to prevent anterior translation of the tibia. ACL injuries most commonly occur without contact and occur with 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, "unhappy triad," after a valgus force is applied to a planted foot. The patient may report a "pop" sensation followed by significant swelling. Delayed presenters complain of a feeling of instability or "giving way" of the knee. Female athletes are at a higher risk for ACL injuries compared to male athletes secondary to an increased Q angle and quad/hamstring muscle imbalance and decreased knee and hip flexion with landing and hormone status [32].

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 a lateral force to the knee that creates a valgus stress. Patient's will complain occasionally of instability but will most often complain of swelling and pain along the medial joint line.

Lateral collateral ligament (LCL): LCL injury is uncommon, but when it does occur is often associated with a PCL injury. Excessive anteromedial knee force when the knee is fully extended can stress the LCL. Patients will sometime complain of lateral leg numbness and weakness with ankle dorsiflexion secondary to associated perineal nerve injury.

Physical Exam

ACL: Examination for potential ACL injury is best done immediately after the suspected injury before subsequent hemarthrosis and muscle guarding limit your examination. Significant

knee effusion will occur within hours of injury. The most accurate diagnostic test of an ACL injury is the Lachman test with a sensitivity of 85 % and specificity of 94 % [33]. Anterior drawer test is not as reliable and can be falsely positive secondary to a PCL injury. Meniscal integrity should also be checked as significant ACL tears have associated meniscus tears.

PCL: Examination will show an effusion and tenderness within the popliteal fossa. Posterior drawer is the assessment of choice. If posterior drawer test is positive, Dial's test should be completed to evaluate for posterolateral corner (PLC) injury. Positive MCL/LCL testing at full extension is also suggestive of a PCL injury.

MCL/LCL: Assess for laxity in these ligaments with the knee in full extension and at 30° of flexion with varus and valgus stress testing. Generally, these patients have less swelling and instability, rather complain of pain over the ligament, and have an appropriate mechanism of injury.

Imaging

X-rays should be obtained to assess for fractures. MRI is indicated in suspected ligament or meniscal tears.

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. A range of motion exercises should be started as soon as pain allows. Referral to orthopedics for discussion of operative should be made but is not emergent as surgery is often delayed 3–6 weeks to allow resolution of hemarthrosis.

PCL: Surgical management is deferred unless other associated injuries such as a posterolateral corner 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 [31].

MCL/LCL: Initial management includes RICE and physical therapy. Grade 3 injuries should be evaluated by an orthopedist, as they are often associated with other soft tissue injuries such as meniscal, PCL, or PLC injuries.

Meniscus Tear

History

A meniscus tear occurs from a traumatic forceful twisting or hyperflexion of the knee. Meniscal injuries are also associated with other traumatic injuries such as ACL and PLC 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 the most common finding on examination. Specialized tests including McMurray test, Apley's Compression test, and Thessaly test can assist in diagnosis.

Imaging

Knee x-rays should be obtained to assess for associated fracture especially in the acute setting. If surgical intervention is being considered, then an MRI is warranted as it is 93 % sensitive and 95 % specific for evaluation of meniscal tears [34].

Management

Rest, ice, activity modification, and physical therapy will treat most chronic meniscal injuries. Steroid injections can be considered to assist in pain

management during physical therapy. Failure to progress with physical therapy and chronic tears that cause true mechanical symptoms should be referred to orthopedics for discussion of operative management. Acute traumatic meniscus injuries often require operative management.

Achilles Tendon Rupture

History

With Achilles tendon rupture, a patient will complain of a sudden pop or snap sensation in their posterior ankle followed by significant pain. Basketball players describe the sensation of someone stepping on their heel.

Physical Exam

Significant ecchymosis will be present over the posterior lower leg. A palpable defect may be palpated over the distal Achilles tendon. Thompson test is the diagnostic test of choice. To complete the test, the patient is placed in the prone position, the knee flexed to 90°, and the gastrocnemius is squeezed. In a negative test (no full substance tear) the patient's foot will plantar flex. With a partial tear, the Thompson test may be positive or negative [35].

Imaging

MRI is the imaging modality of choice. MSK ultrasound is another imaging option.

Management

Initial management includes splinting with a posterior splint with the ankle in plantar flexion. All patients need referral to orthopedic surgery for discussion of definitive management.

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 at the calcaneus or 3–5 cm proximal to the insertion [36]. 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 expressed as well.

Physical Exam

Little to no 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 will be noted secondary to tight gastrocnemius/soleus complex. Pes planus can also be seen on exam.

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.

Management

Treatment depends on the location of symptoms. Initial management includes RICE and activity modification. Heel lifts should be added to the patient's shoes along with ensuring the underlying pes planus is addressed with appropriate orthotics. Very good evidence exists for the treatment of mid-substance tendinopathy with intense eccentric rehabilitation programs. Unfortunately, insertional tendinopathy is more difficult to treat. Eccentric rehabilitation protocols can be

attempted but have not been as successful as with mid-substance disease. If the patient fails to demonstrate any improvement with conservative treatment and a short course of therapy, immobilization in a walking boot with heel lift is often needed for 4–6 weeks prior to reinitiating eccentric rehabilitation. Steroid injections should be avoided in the management of Achilles tendinopathy given the associated increase in tendon rupture [35, 36].

Ankle Sprains

History

Ankle sprains can be broken down into lateral, medial, or syndesmotic "high ankle" sprains. Lateral injuries occur when a plantar-flexed ankle is inverted. Inversion injuries will most commonly damage the anterior talofibular ligament (ATFL). This type of injury is common in basketball, soccer, or football. Medial ankle injuries are not common and involve eversion of a plantar-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 and will damage the anterior interior tibiofibular ligament (AITFL). Disruption of the AITFL can lead to disruption of dense connective tissue between the tibia and fibula, i.e., syndesmosis. For all the types of injuries, 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. Palpation should occur over the bony landmarks of the Ottawa ankle rules; these landmarks include the posterior aspect of the distal one third of the distal lateral malleolus, posterior aspect of the distal one third of the medial malleolus, navicular bone, and base of fifth metatarsal. Palpation over the main ligaments of the ankle (ATFL, AITFL, calcaneofibular ligament (CFL), posterior talofibular ligament (PTFL), and the deltoid ligament). Tenderness over the ATFL is often found on lateral ankle injuries.

Several special tests exist for the ankle. The anterior drawer test and the talar tilt test can be used to assist the diagnosis of lateral ankle sprains. For high ankle sprains, the external rotation test, tenderness over the AITF, and the squeeze test should be done to confirm diagnosis.

Imaging

Initial examination in an ankle injury should include evaluation of the ankle for the need to obtain an x-ray. This can be done using the Ottawa ankle rules which help to reduce the number of unnecessary x-rays by 30–40 % [37]. The Ottawa ankle rules have been validated for a patient as young as age 5 and demonstrate almost 100 % sensitivity [38]. X-rays are indicated if any of the following five physical exam findings are present:

- Inability to bear weight for four steps immediately after the injury or in the exam room
- Bony tenderness over posterior aspect of the medial malleolus
- Bony tenderness over posterior aspect of the lateral malleolus
- Bony tenderness over 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 in syndesmotic injuries and lateral malleolus fractures. Providers should consider obtaining additional plains of the proximal tibia and fibula on high ankle sprain patients with a positive squeeze test to evaluation for a possible Maisonneuve fracture of the proximal fibula.

Management

Grade 1 and 2 lateral and medial ankle sprains should be treated with rest and ice. A range of motion exercises or formal physical therapy should be initiated within the first 48 h. These injuries will typically heal in 1–4 weeks. Grade 3 injuries may require 5–7 days 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 [37, 38]. Significant medial ankle injuries can take several months to fully rehabilitate. Surgical referrals to orthopedics should be reserved for chronic pain, chronic instability, and inability to return back to previous functional level after an appropriate rehabilitation course. Consideration should be made for athletes to wear a lace-up ankle brace with Fig. 8 straps after returning to competition [37, 38].

High ankles 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 severity of 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.

Proximal Fifth Metatarsal Fracture

History

A patient will either describe an acute injury from an inversion injury or blunt trauma or a history of dull pain with sudden increase in pain. The most common mechanism of injury is adduction of the foot while in plantar flexion. This can occur from a direct force to the lateral side of the foot and/or landing on the side of the foot after stumbling. 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.

Imaging

Standard AP, lateral, and oblique radiographs of the foot are usually sufficient. If 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. Proximal fifth metatarsal fractures are subdivided into zone 1, zone 2, and zone 3 injuries. Zone 1 injuries are avulsion injuries that occur at the styloid. Zone 2 fractures occur at the metaphyseal-diaphyseal junction, while zone 3 fractures occur in the proximal diaphysis [39].

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 or a CAM walking boot for 3–4 weeks. Zone 2 injuries are also known as Jones fractures. Malunion and nonunion complications can occur with both operative and nonoperative management, approximately 20 % with each [40]. Conservative management includes 6 weeks of non-weight bearing in a short leg cast followed by 6 weeks in a weight-bearing short leg cast. After 12 weeks of immobilization, the patient can be transitioned into a CAM walking boot or lace-up ankle brace depending on radiographic and clinical healing. 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 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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Care of the Obese Patient

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General Principles

Epidemiology

In 2014 more than one-third of adults (78.6 million) in the United States of America (USA) were obese with annual costs for obesity estimated at $147 billion in 2008 US dollars [1]. The overall prevalence of obesity in the USA doubled between 1994 and 2014, and the prevalence of extreme obesity rose from 3.9 % to 6.6 % between 2000 and 2010 [2]. Childhood obesity has more than tripled in the last 40 years from 5 % between 1963 and 1970 to 17 % in 2003–2004, although the rate has stabilized in children in the last decade [1, 3]. Obesity rose from a prevalence no greater than 14 % in any state in 1990 to no state having a prevalence less than 20 % in 2010, with the national average at 34.9 % [4] (Fig. 1). This rapid increase has led to an alarm of an "obesity epidemic." In 2013 the American Medical Association initiated designation of obesity as a disease "requiring a range of medical interventions to advance obesity treatment and prevention" and "help change the way the medical community tackles this complex issue" [5].

Racial and socioeconomic disparity in obesity rates is clearly evident in children, adolescents, and adults. Among US adults, non-Hispanic blacks have the highest age-adjusted rate of obesity (47.8 %), followed by Hispanics (42.5 %), non-Hispanic whites (32.6 %), and non-Hispanic Asians (10.8 %) with a similar racial trends in

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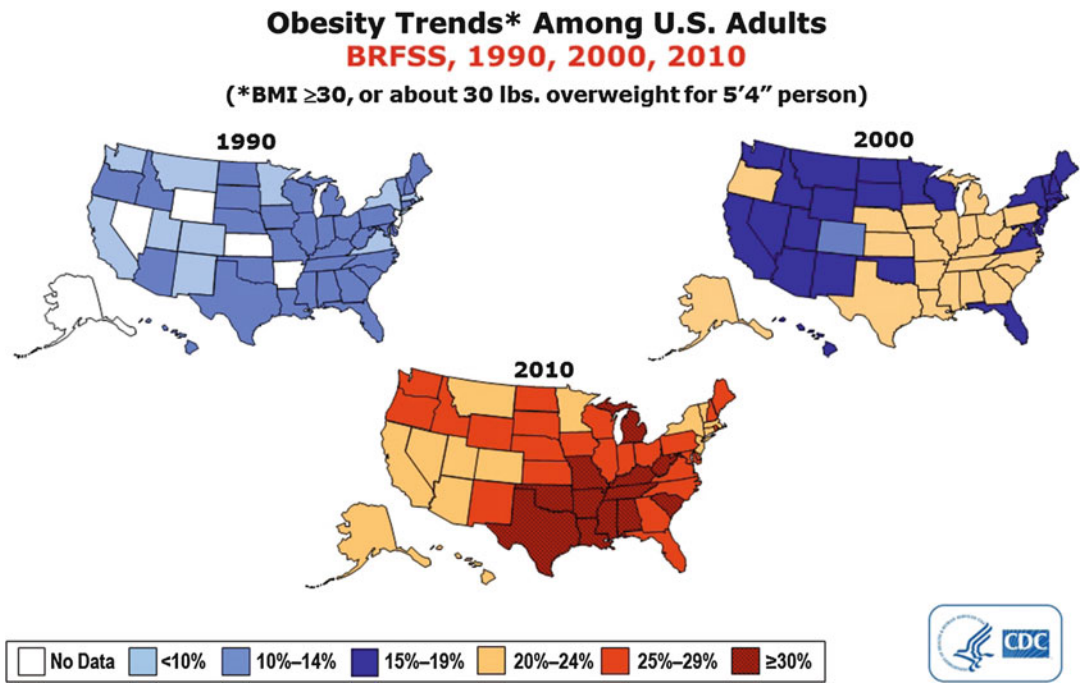

Fig. 1 Prevalence of obesity (BMI $\geq$ 30 kg/m^2) among US adults ages from 1990 to 2010 [4]. CDC's Obesity Prevalence maps, available at: http://www.cdc.gov/obesity/data/prevalence-maps.html. Abbreviations: *BMI* body mass index

children and adolescents except that Hispanic youth have a greater incidence of obesity than non-Hispanic black youth (22.4 % vs. 20.2 %) [1]. Income and educational status have both been associated with trends in obesity, but the specific effects vary between races and gender. These medical disparities highlight the need for individualized treatment plans that factor in cultural and social realities.

Effects

Obesity has long been known to be associated with or increase the risk of developing many of the most common chronic diseases (see Table 1) and has been shown to increase risks of both cardiovascular disease (CVD) mortality and all-cause mortality [6].

The converse is also true in that even a modest weight loss of 3–5 % has been found to improve outcomes for some cardiovascular risk factors including progression of diabetes and hypertension, with larger weight loss resulting in greater benefits [6].

Definition

Obesity is a disease condition of excess body fat that may put a person at health risk [1, 7], but in reality percentage body fat is a difficult thing to measure. Thus, worldwide the definition of obesity is based on body mass index (BMI). Population studies have consistently shown that when BMI is viewed as a continuous variable, all-cause mortality steadily increases above a BMI of 22 kg/m^2, and recent guidelines support the current cut points for defining overweight and obesity [3, 8]. BMI is calculated by dividing a patient's weight in kilograms by their height in meters squared (kg/m^2). Simple web-based calculators and apps are widely available, and most

Table 1 Obesity-associated comorbidities and complications by organ system

Obesity-Associated Comorbidities and Complications by Organ System [7,8]		
Cardiovascular		
Heart disease		
Hypertension		
Dyslipidemia		
Congestive heart failure		
Cardiovascular disease death		
Stroke		
Endocrine		
Type 2 diabetes mellitus		
Reduced fertility		
Gastrointestinal		
Barrett's esophagus		
Cholesterol gallstones		
Hiatal hernia		
Reflux disease		
Musculoskeletal		
Injuries/Fractures[a]		
Osteoarthritis		
Pain[a]		
Neoplasms		
Breast	Endometrium	Ovaries
Cervix	Kidney	Prostate
Colon	Liver	Rectum
Psychological		
Depression		
Discrimination		
Emotional distress		
Impaired psychological functioning[a]		
Social stigmatization		
Reproductive		
Amenorrhea		
Infertility		
Menorrhagia		
Negative fetal outcomes		
Increased maternal complications		
Respiratory		
Asthma[a]		
Obesity hypoventilation syndrome		
Sleep Apnea		
Urological		
Stress Incontinence		

[a]Pediatric complications

EMRs are now configured to automatically calculate BMI from the height and weight values.

In adults, obesity is diagnosed in those with a BMI over 30. Overweight and obesity are subdivided as follows: BMI 25–29.9 (overweight), BMI 30–34.9 (class I obese), BMI 35–39.9 (class II obese), and BMI > 40 (class III obese or "extreme obesity") [6]. In children, obesity is based on BMI percentile in reference to CDC growth charts. High BMI in children has been found to predict future adiposity, morbidity, and death leading to recommended diagnostic terminology of children being "overweight" when their BMI is between 85th and 94th percentiles and "obese" when their BMI is at or above the 95th percentile [3].

Etiology

Obesity is the result of a chronic imbalance between energy intake and energy expenditure leading to the storage of excess energy as fat, primarily in white adipose tissue [8]. However, the underlying reasons for this imbalance are multifactorial and complex and include genetic makeup, cultural beliefs, environment, habits, physical activity, dietary intake, and occupation [7, 8]. Contrary to social stigmatization, evidence supports that obesity is not simply a problem of the lack of willpower or self-control, but stems from a disordered regulation of appetite and energy metabolism associated with a variety of comorbid illnesses [7].

Weight homeostasis involves a complex and redundant neurobiological system with signaling primarily between the central nervous system,

adipose tissue, and the gastrointestinal (GI) system to regulate metabolic rate and drive eating behavior [8]. Recent research has focused on peripheral signaling hormones that seem to promote satiety or decreased food intake in hopes of designing therapies to combat obesity or assist with weight maintenance. Anorexigenic hormones secreted from the GI system (cholecystokinin (CCK), pancreatic polypeptide, peptide tyrosine-tyrosine (PYY), glucagon-like peptide-1 (GLP-1), and oxyntomodulin) and adipokines (leptin, adiponectin) produced by white adipose tissue are potential candidates. Research has uncovered that most markers of satiety are reduced and most measures of appetite enhanced in patients who have lost weight, which partly explains the difficulty patients experience in sustaining weight loss [8].

Yet, while "nature" plays a clear role, "nurture" is also at work. The demographics in western societies have shifted over the last half century from that of a largely rural population frequently involved in manual labor to a heavily urban demographic with more sedentary lifestyles. Compounding this are vast changes in food – both in quantity and in kind. Highly processed foods have become widely available and some of the lowest costing foods are calorie dense and contain high levels of fat, sugar, and salts.

Diagnosis

History

Obesity is overwhelmingly a primary process: imbalance of caloric intake to caloric expenditure. As noted, there are myriad reasons for this imbalance, but elucidation of individual factors can be an intensely sensitive topic. Review of a patient's weight trajectory plotted over time, typical caloric intake, and typical physical activity can be used to guide initial work-up of obesity and subsequent office-based recommendations. Further insights can be gleaned when the patient annotates significant life occurrences (i.e., employment changes, tobacco cessation, end in a relationship, etc.) on the weight trajectory timeline. Ideally, patients complete oral intake diaries recording all beverages, meals, snacks – anything a patient puts in their mouth – as well as daily physical activity including the time.

As obesity usually derives from a primary etiology, work-up for secondary causes of obesity in adults should be based on specific symptoms or risk factors coupled with a physician's index of suspicion. Medications should be reviewed for potential obesogenic medications as some common drug classes are clearly associated with weight gain including atypical antipsychotics, anti-depression medications, and diabetic medications. History should ensure there is no comorbid psychiatric illness leading to weight gain such as eating disorders, depression, or body dysmorphia, and in women a detailed menstrual history should be obtained to evaluate for polycystic ovarian syndrome.

Physical Exam

Appropriate height and weight are paramount in children and adults alike. Additional screening of waist circumference in adults with a BMI between 25 and 35 may be undertaken as such individuals have an elevated CVD-related and overall mortality if their waist circumference is $>$102 cm (~40 in.) for males and 88 cm (~35 in.) for females [6]. Measuring waist circumference when BMI is greater than 35 is generally not indicated as such patients can be expected to have increased waist sizes. Physicians should also have a keen eye for physical markers associated with the uncommon causes of secondary obesity including acanthosis nigricans, goiter, moon faces, buffalo hump, central obesity, striae, and hirsutism.

Additional Testing

Most lab testing is geared toward evaluating for comorbidities of obesity rather than ruling out causes. Screening for impaired fasting glucose or frank diabetes (fasting glucose), nonalcoholic fatty liver changes (AST/ALT), and dyslipidemia to complete cardiovascular risk assessment (lipid

panel) is appropriate at least biannually starting at age 10 [3]. While thyroid disease is associated with obesity, TSH is of limited benefit even in adults and is not recommended as a screening test in the pediatric population. In the pediatric population, lab tests ought be performed only in those with short stature (<5th percentile), developmental delays, dysmorphic features, or who have clear signs or symptoms of underlying endocrine abnormalities especially as cortisol, and TSH levels are often elevated in children with obesity [9].

Treatment Plan

In 2013, a seminal Guideline for Management of Overweight and Obesity in Adults was authored collaboratively between the American College of Cardiology (ACC), the American Heart Association (AHA), and The Obesity Society (TOS) and includes an evidence-based treatment algorithm with recommendations on the management of patients with overweight and obesity. After diagnosis of obesity, or overweight with comorbidities, physicians are encouraged to assess for patient willingness to change. Once patients are committed to weight loss, a "high-intensity comprehensive lifestyle intervention" becomes the cornerstone of therapy – with or without adjunct use of pharmacotherapy or surgery [6]. Such an intervention is defined as being greater than or equal to 14 face-to-face sessions in a 6 month time frame and includes three principle components: a moderately reduced calorie diet, an increased physical activity program, and the use of behavioral strategies to better comply with the diet and exercise programs [6].

Dietary Management of Overweight and Obese Patients

In today's targeted consumer-based market, new diets appear almost every season claiming to be more effective than their predecessors. Certain diet plans focus on altering macronutrients, while others emphasize creating a negative energy balance through cutting overall calories. Combination plans combine diet type (i.e., low carbs) with behavior interventions, such as group meetings, calorie counting, or food journals. Patients often want quick results which are often impractical, lead to treatment failures, and cause patient dissatisfaction.

Recent meta-analysis of 48 original RCTs showed overweight and obese adults randomized to any popular diet or meal replacement plan lost significant weight at 6-month and 12-month intervals (approx. 8 and 7 kg, respectively), on any low-carbohydrate or low-fat diet [10]. Thus, the landmark 2013 guidelines by the ACC/AHA/TOS encourage physicians to recommend a weight-loss diet based on patient adherence rather than the diet type [6]. A daily energy deficit of greater than 500 kcal can usually be accomplished with 1,200–1,500 kcal/day for women and 1,500–1,800 kcal/day for men, but very low-calorie diets (800 kcal/day) should be confined to patients within a medical care setting where close medical monitoring and high-intensity lifestyle interventions are available [6].

There may be benefits to a diet beyond weight loss, and dietary composition may affect cardiovascular biomarkers (triglycerides, HDL cholesterol, glucose, and insulin) [11], whether through loss of adipose tissue or an independent mechanism. Data published over the last decade touted that Mediterranean-type diets – those rich in nuts, whole grains, vegetables, poultry, and fish instead of red meats – may help patients achieve better glucose or insulin control. However, a 2014 systematic review showed no difference between diet types (low carbohydrate vs. isoenergetic balanced) in overweight and obese adults when it came to preventing or reducing cardiovascular risk factors (blood pressure, lipids, and fasting blood glucose) [12].

Exercise

Patients often resort to increased physical activity and binge exercise as a weight-loss tool, but data shows that these measures only result in modest weight loss, even over the long term. Moderate

intensity aerobic exercise programs have been shown to net participants 1.7 kg (3.7 lbs) weight loss versus controls over 12 months, and exercise also increases weight loss in those dieting by an additional 1.1 kg (2.4 lbs) [13]. Exercise of any intensity can improve cardiovascular outcomes and metabolic profiles, but results vary for each patient and activity. Similar to recommending a diet, family physicians should encourage patients to partake in activities of moderate intensity that are enjoyable and those to which the patients will adhere.

Pharmacological Management of Obesity

There are several pharmacological agents approved by the Food and Drug Administration (FDA) for use in the short- (<12 weeks) and long-term (>52 weeks) management of obesity. Such agents have various targets and mechanisms of action and include two new medications approved by the FDA in 2012. Physicians should view medications as adjunctive therapy to other interventions, started when initial management strategies including diet, exercise, and intensive behavior therapy fail to yield clinical results. Weight-loss drugs have a long and tarnished history, with many drug recalls and associated adverse events, especially increased cardiovascular risks. Pharmacotherapy should be discussed with patients as early as at the first encounter, including various options, side effects, and any associated adverse events. As with any other therapeutic interventions, physicians need to monitor compliance, respond to treatment, and manage expectations carefully. Significant weight loss can take over a year, and most patients will regain some weight after an initial period of response.

Pharmacotherapy alone is not more effective than diet and exercise; however, when used as adjuvant therapy, physicians and patients can expect to see significant results over the long term. Table 2 summarizes agents currently approved by the FDA for weight loss, along with dosing info, weight-loss results, and most commonly reported adverse events.

Surgical Management of Obesity

Surgical treatment for obesity has been around since the 1950s when it was incidentally discovered that procedures resulting in restriction, size limitation, or malabsorption syndromes of the gut (i.e., gastric and bowel resections) led to postoperative weight loss over both the short and long term. These surgeries were initially considered too risky for obesity management due to high rates of complications and significant morbidity and mortality. The field was transformed in 1991 after the NIH Consensus Conference concluded that vertical banded gastroplasty and Roux-en-Y gastric bypass procedures were safe and effective treatment options for morbidly obese patients (BMI > 40 or BMI > 35 with comorbidities present) [23]. The consensus statement, along with the rise of laparoscopy in the early 1990s, led to standardization and advent of safer techniques.

Clinical evidence demonstrates that surgical treatment of obesity results in greater weight loss than any other conventional pharmacological treatment or lifestyle modifications, including diet, exercise, and intensive behavior therapy [24]. The Swedish Obese Subjects (SOS) study showed long-term mortality was lower in the surgical group (>10 year) [25], and several large randomized trials have shown superior efficacy of bariatric procedures for treating T2DM and inducing remission at 2 years [3]. Observational data has shown improvement in quality of life and a decrease in the incidence of diabetes and certain types of cancer [26].

A 2013 meta-analysis directly comparing bariatric surgery with nonsurgical treatments (lifestyle modifications including diet, exercise, and various pharmacotherapy) for obesity concluded that surgical treatment leads to greater body weight loss and higher remission rates of T2DM and metabolic syndrome [27]. This review included 11 trials and looked at the most commonly used open and laparoscopic techniques: Roux-en-Y gastric bypass (RYGB), adjustable gastric banding (AGB), sleeve gastrectomy (SG), biliopancreatic diversion, or biliopancreatic diversion with duodenal switch. Most common adverse events were anemia (iron deficiency) and reoperations [27]. For the best

Table 2 FDA-approved pharmacotherapy for obesity management

	DRUG[(FDA Approval)] *TRADE NAME*	PHARMACOLOGY / DOSING	TOTAL (PLACEBO SUBTRACTED) WEIGHT LOSS & EFFECTS	SIDE EFFECTS[A]
Long-Term (>52 wks)	**Lorcaserin** (2012) *Belviq ©*	Selective 5-HT2C receptor agonist 10mg PO BID	4.5% (3%) after 1 year[14,15] Decrease in BP[16] Decrease in LDL & HgbA1C Appetite suppression	Headache[17] Nausea Fatigue Dizziness URI/Nasopharyngitis Cardiovascular Risk? [B]
	Naltrexone-bupropion SR (2014) *Contrave ©*	Opioid receptor antagonist; DA/NE reuptake inhibitor 8/90 mg ER titrated up to 2 tabs PO BID	6.5% (4.6%) after 1 year[18,19] Reduced food intake Decreased visceral fat and waist size	Nausea Headache Constipation Sleep disturbance Anxiety
	Orlistat (1999) *Xenical ©* *Alli © (OTC - 2007)*	Lipase inhibitor 120mg PO TID (RX) 60mg PO TID (OTC)	11% (5%) after 1 year 6.9% (2.8%) after 4 years[14] Decrease in LDL cholesterol & HgbA1C Prevention of Type II DM (37% RR reduction)	Flatus with discharge[17] Oily spotting Fecal urgency/incontinence Steatorrhea Fat-soluble vitamins deficiency **Approved for use in adolescents**
	Phentermine/Topiramate ER (2012) *Qsymia ©*	Sympathomimetic / anti-epileptic; exact MOA unknown High Dose: 15mg/92mg ER PO QAM Low Dose: 7.5/46mg ER PO QAM	10.9% (9.3%) at 56 weeks for High Dose[20] 5.1% (3.5%) at 56 weeks (Low Dose) Decrease Systolic & Diastolic BP Decrease in LDL and triglycerides	Paresthesia[19,20] Dry mouth Constipation Dysgeusia Insomnia Mood & cognition related events were reported more frequently in High-Dose treatment group
Short-Term	**Phentermine** (1959) *Adipex-P ©; Fastin ©; others*	Appetite suppression via sympathomimetic action 15mg - 37.5mg PO ONCE DAILY	Paucity of long term trial data to establish weight-loss compared to baseline	*CNS:* insomnia, elevation in heart rate, dry mouth, taste alterations, dizziness, tremors, headache, anxiety, and restlessness *GI:* diarrhea, constipation, and vomiting
Novel Agents	**GLP1-Receptor Agonist** *Liraglutide © - approved for T2DM*	Appetite suppression via GLP1-R agonism *Dose ranges in Phase II / III trials* 1.8mg to 3mg PO ONCE DAILY	8% (5.4%) after 1 year[16] Improvement in plasma glucose[16] Decrease in systolic BP Decrease in triglyceride concentration	Nausea[16] Vomiting Constipation Diarrhea Headache Unclear association with pancreatitis
	Peripheral MetAP2 Inhibitors *Beloranib © (Phase III)*	Peripheral inhibition of angiogenesis in adipose tissue; stimulates energy expenditure, fat utilization, and lipid excretion[21] 0.9 mg/m2 IV TWICE WEEKLY for 4 weeks	3.5% (2.9%) after 4 weeks[21] Appetite suppression[21] Decrease in Triglyceride concentration Decrease in CRP levels	Headache; infusion site injury; nausea; diarrhea

A) In order of frequency reported in randomized trials.
B) Valvulopathy-rates, as seen on echocardiography, were similar in treatment and placebo group at 1 year but FDA has requested a post-approval trial to see long term cardiovascular effects.[16,22]

[a]In order of frequency reported in randomized trials
[b]Valvulopathy rates, as seen on echocardiography, were similar in treatment and placebo group at 1 year, but FDA has requested a post-approval trial to see long-term cardiovascular effects [16, 22]

outcomes, it is recommended that patients be sent to specialty hospitals that perform high volumes of bariatric cases annually.

RYGB has a greater cardiovascular mortality risk reduction and leads to much greater weight loss compared to AGB at 2 years but has a higher risk of short-term (30 days) complications [28]. Some high-volume bariatric surgery centers are able to achieve similar weight loss at 2 years following either ABG or RYGB [P24]. AGB may appear to have a lower rate of short-term risk, but the procedure has a rate of band removal as high as 50 % due to "failure to achieve or maintain clinically significant weight loss; band malfunction, slippage, or erosion; or patient intolerance of the gastric restriction" [29].

Although SG is fast becoming one of the most common bariatric procedures [30], there is limited long-term outcomes data; ongoing trials are expected to yield results in the near future on long-term outcomes data [24]. A Cochrane Review© published in 2014 showed similar

weight-loss results (based on BMI at 2-year follow-up) after either SG or RYGB [28]. Endoscopic techniques are a novel treatment option in the past few years, but again there is a paucity of outcomes data at this time. Endoscopic sleeve gastroplasty (ESG), which aims to reduce gastric volume via placement of full-thickness sutures, showed weight loss of 30 % in 10 patients at 6 months, with no significant adverse events [31].

A big challenge for the primary care physician is deciding when to refer a patient to a surgeon for this invasive and life-altering treatment. As with any other surgical treatment, patients need to be made aware of all the risks and benefits and both short- and long-term complications. There is limited long-term data on aspects of bariatric surgery not related to weight loss, including mental health and reproductive outcomes, or for long-term management of complications due to weight loss [15]. Patients having undergone bariatric surgery are advised long-term follow-up and ongoing nutrition and lifestyle management to monitor for any nutritional deficiencies [29].

Prevention

In obesity, an ounce of prevention may well be worth more than a pound of cure given the clinical realities experienced by those trying to lose and maintain weight loss, not to mention the potential risks of medication or bariatric surgery. A focus on promoting healthy weight in those who are normal weight or overweight may be a more profitable strategy, especially when focusing on children. Family physicians can leverage their understanding of the familial realities in helping individual patients and their families arrive at healthful lifestyle measures that will prevent obesity. Consistent evidence supports family physicians recommending limiting consumption of sugary beverages, limiting screen time (2 h max in children over age 2), limiting eating out, limiting portion size, promoting regular consumption of breakfast, and promoting eating family meals together [3].

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Family Medicine
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Care of the Difficult Patient

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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]. It is estimated that 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.

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." 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 [5]. 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) [6]. Physicians must approach patients with inclusion, characterized by personal engagement, and availability, an openness to learn about others' experiences [7].

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 [8]. Patients identified physician communication, respect for the patient, sympathy, empathy, patient-centeredness, and shared decision-making as important elements that were sought in doctor/patient interactions [9].

The value of effective doctor/patient relationships includes improved trust, commitment and adherence to care recommendations [10], and effective relationships result in improved healthcare outcomes including biomedical markers, behavioral outcomes, and improved communication between physicians and patients [11, 12].

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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" were also found to be 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 high levels of impairment of 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" [13].

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 [14]. Physicians have further identified patient behaviors that characterize difficult encounters, including insisting on an unnecessary medication, showing dissatisfaction with care provided, etc. [15]. In one study in a resident clinic, poor social support on the part of patients was also associated with problematic doctor/patient relationships [16]. 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 [17].

Diagnosis

In 1978, Groves identified four types of "difficult" (or, as described in the article, "hateful") patients and characterized them as noted below [18]. Although the language is inappropriate in today's patient-centered approach to care, the categories still have value and may serve as archetypes to facilitate initial approaches to caring for these patients. A reevaluation of this model updated for the twenty-first century [19] highlights the fact that these four general categories are still relevant today. The update notes that illness and disease can be considered a direct threat to the patient's wholes and integrity, and this threat causes individuals to turn to behaviors or coping mechanisms that may not be beneficial of 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 that 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 [19] by noting that in this case patient's goal is the relationship with the physician as opposed to a cure.

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- Self-destructive "deniers": these patients are described as continuing behaviors that actively contradict or undercut physicians' attempts to help them, and that they 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 [20]. 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 [21], 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 patient 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. Special problems that are difficult to address, such as substance abuse, chronic pain, etc. [22]

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 is part of the visit and that shared decision-making is a focus of each visit.

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 [13]. Physicians working in health maintenance organizations (HMOs), as opposed to private practice, and primary care physicians have indicated higher levels of frustration [22]. 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 [15]. 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" [23]. 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 [24].

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

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questions, or if physicians are not giving enough medical information [25]. 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 [26]. 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 [27].

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 [28]. This model may be used to consider how to approach a difficult patient/physician 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: 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 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

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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.

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 mental health evaluation and care and that using Kleinman's explanatory model [29] may help enhance communication between physician and patient [3], especially if there are discordant views of the patient's health status.

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 via behaviors such as reluctance to accept recommendations, interrupting the physician, "by the way" statements as a visit closes, etc. [30]. 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 and can 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 [31]. 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 [13].

Building out of the four "hateful" patients he described [18], 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 [21]. 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 [14].

At any point a physician may notice that 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 [27]. This stepwise approach may help avoid conflict and tension and may minimize the experience of difficult interactions between patients and physicians.

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

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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. [32]

focuses on physician responses to difficult encounters while seeing to preserve the relationship [32]. 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 [17].

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 [33].

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 [34].

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 [19].

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 relationship should look like: a shared commitment to investigating ultimate causes of both the current illnesses as well as 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 [35]. 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,

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Table 2 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

etc.), and in promoting endurance and satisfaction [36]. 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 [37], 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 have 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 2). In a randomized trial, using BREATHE OUT improved physician satisfaction with challenging patient visits [38].

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].

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 [18]. 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 them. "Difficult" patients are also less likely to be satisfied with their healthcare and to seek more medical visits and interventions [13], suggesting that finding effective ways to work with challenging patients can lower healthcare utilization

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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 [15]. 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

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Contents

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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 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 use 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.

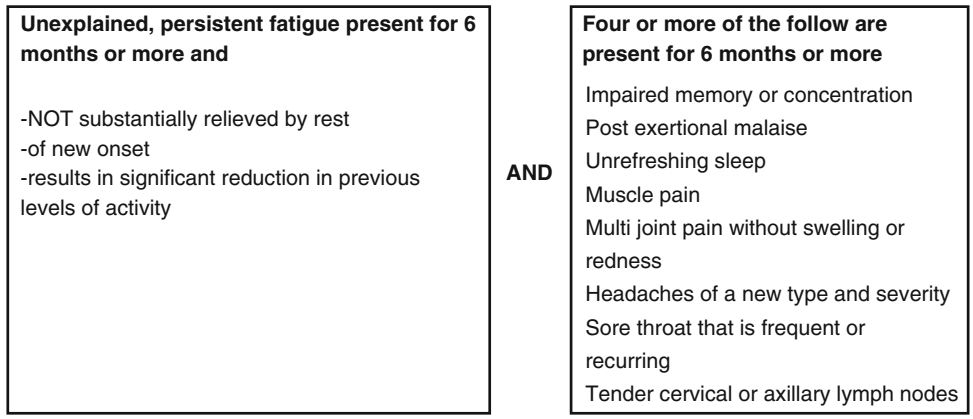

Fig. 1 CDC criteria for diagnosing chronic fatigue syndrome [4]

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 also 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 is one of exclusion, requiring the family physician to rule out other conditions that can present with similar symptoms. Diagnostic criteria published by the CDC in 1994 offer a framework upon which to evaluate patients with long-standing fatigue [4]. These criteria, which were initially developed for the purposes of defining a specific population for research, are also helpful to the family physician considering the diagnosis of CFS (Fig. 1).

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 [4]. It is also important to consider the medical and psychosocial context within which the fatigue developed as well as prior history of trauma and the social support system of the patient [5]. 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.

Complete blood count with differential
Basic Metabolic Panel
Calcium
Phosphorous
Liver function tests (including AST, ALT, 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

Fig. 2 Tests to consider in evaluating for underlying causes of fatigue [4, 6]

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 [6] (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. If the patient does not meet all of the criteria for CFS but no other etiology has been determined the diagnosis of idiopathic chronic fatigue or a CFS-like illness can be made [4].

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 [7]. For example, patients who participated in support groups had a lower 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 [7]. 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.

CBT

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 [5, 6]. GET is thought to work synergistically with CBT because it provides a practical context for the cognitive restructuring around fatigue that effective CBT encourages [9]. 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 [9]. 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. [9] 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 [5, 6, 10]. 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 in an effort to gain relief from their symptoms. [10] 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 have an effect on 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 [11].

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 [6].

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 play a large role in determining their response to treatment of any kind; patient engagement and activation is absolutely critical to success [3].

CFS 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, US, and British populations [12]. 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 [12]. Making a prompt diagnosis and getting children and adolescents into the appropriate treatment is of the utmost importance, as these determine the prognosis for the child's recovery [12].

CFS in Elderly Adults

Fatigue is a prevalent concern in the elderly with some estimates of prevalence greater than 70 % [13]. 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 and/or laboratory evaluation [13]. 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.

CFS 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 [14]. 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 [14].

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 is one way 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 created by the CDC. 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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Contents

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General Principles

Definition/Background

We each spend 1/3 of our lives in the reversible state of perceptual isolation that we call sleep. Unsurprisingly, disruptions and disorders of this primary physiologic state can lead to declines in quality of life, diminished waking performance, more frequent illness, as well as increases in disease morbidity and mortality. The spectrum of sleep disorders mirrors the clinical population of patients seen in a family medicine practice with most patients with sleep disturbance receiving their medical care in the primary care setting [1]. Despite a high prevalence of sleep disorders, sleep complains are 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 reducing morbidity and mortality, improving comorbid disease processes, and improving 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 affects on waking performance 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 a 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 most at risk include women and older adults. The insomnias include the complaint of difficulty with sleep initiation, duration, consolidation, or quality, associated with daytime functional impairment. The daytime functional impairment in insomnia includes fatigue, impaired memory or concentration, mood disturbance, daytime sleepiness, reduced motivation or energy, tension, headaches, or gastrointestinal symptoms. In adults, chronic insomnia is associated with impaired social and vocational function and reduced quality of life and in severe cases may be associated with an increased risk of traffic and work site accidents as well as psychiatric disorders. In pediatrics, insomnia is particularly a problem around the age of two when the child first attempts to sleep independently of parents [6].

Individuals with chronic insomnia consistently report lower values of quality of life particularly 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 cost and health-care utilization data calculated for insomnia includes annual direct costs in the United States which include $1.97 billion for medications and 11.96 billion for health-care 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. The diagnosis of the insomnias is primarily based on a sleep history. 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). Physical exam contributes little to the diagnosis or evaluation of insomnia. 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 newer hypnotic agents are less likely to have deleterious side effects than most OTC treatments for insomnia [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 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 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 improvements in associated sleep states and daytime performance	C	Consensus guidelines, usual practice

Adapted and updated table from Pagel and Pegram [9]
Strength of recommendation based on Ebel et al. [10]

The Sleep-Associated Breathing Disorders

Background

Obstructive sleep apnea (OSA) is one of the most physiologically disruptive and dangerous of the sleep diagnoses. Recent epidemiological studies demonstrate that OSA has a strong association with pulmonary, cardiac, endocrine, and cognitive disease [12]. In patients with OSA, continued breathing effort occurs despite obstruction of the airway resulting in inadequate ventilation. OSA is more common among men, those who snore, are overweight, have high blood pressure, or physical abnormalities in their upper airways. Worldwide, more than 700 million individuals now have a BMI $>$ 30 and meet criteria for obesity [9]. This level of obesity and an increasingly aging population have resulted in a situation in which we are currently experiencing 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 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 4).

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)
Nonattended 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)
Autotitrating PAP for treating obstructive sleep apnea	B	Case control studies with good follow-up
Multiple sleep latency testing indications (a) Assessing daytime sleepiness (b) Diagnosing narcolepsy	B	Meta- analysis, usual practice, usual practice, and disease-oriented evidence

Adapted table from Pagel and Pegram [9]

Adult OSA has a clear association of daytime cognitive impairment (i.e., daytime sleepiness) that leads to a significant increase in 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] (Table 5).

Table 4 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 – 60–95 %

Diagnosis and Treatment

OSA most often requires polysomnography (PSG) testing for diagnosis and treatment. PSG is the recording of multiple physiological signals during sleep including channels of electroencephalography (EEG), electrooculogram (EOG), and chin electromyogram (EMG) that are required for 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 act as a pulmonary splint keeping the airway open during sleep by utilizing positive airway pressure

Table 5 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
	Diabetes	C – retrospective cohort studies
	Other cardiac arrhythmias	C – case series, usual practice
Pediatric OSA	Poor school performance	B – multiple retrospective cohort studies
	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]

(PAP). This treatment is well tolerated by most OSA patients with few side effects and documented reductions in morbidity, hospitalization, and health-care utilization [16]. In evaluating OSA, a split night protocol is often utilized in which a therapeutic treatment or "titration" portion of the PSG is added after a period of diagnostic sleep time. A PSG interpretation should include 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 of any treatment attempted during the night of study.

Sleep laboratory testing can be expensive, and alternative approaches are now often utilized. OSA is now commonly initially evaluated using home screening tests (HSTs), an approach that has been shown to be particularly useful in younger patients without comorbid diagnoses [17]. These studies have limitations. They cannot determine whether the patient is actually asleep during the recording, and in patients with insomnia and those with ongoing psychiatric problems, the number of respiratory events (apneas and hypopneas) per hour will be lower than actually present due to the large amount of recording time that will be in wake. Periodic limb movements and arousals from events such as parasomnias are not recorded by HSTs. Most home screeners differentiate poorly between obstructive and central apneas. Central sleep apnea (CSA) includes nonobstructive apneas in which respiratory efforts do not occur. CSA is present most often in patients with a history of 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 [18, 19]. Treatment includes oxygen or systems that incorporated backup rates in addition to PAP.

By coupling HST with autotitration treatment, patients with OSA can avoid any form of full PSG testing. Autotitrating 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 [20].

The pathophysiology and clinical presentation differ for pediatric OSA. In pediatric patients, OSA is most clearly associated with tonsillar hypertrophy. OSA can contribute to poor school performance [21]. Studies also support the association of pediatric OSA with failure to thrive, obesity, enuresis, attention deficit/hyperactivity disorder, 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 1.5 % of police-reported crashes and 4 % of all traffic crash fatalities involved drowsiness and fatigue as principal 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 [22]. 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) [23]. The next most common cause is untreated OSA. The other sleep disorders that induce daytime sleepiness occur at a much lower frequency. 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 (a diagnostic criteria for narcolepsy). Narcolepsy is the most common of the neurological diseases inducing severe daytime sleepiness, present in 1-2/1000 of the general population. Medications that are 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 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 approx 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 [24]. Jet lag and shift work disorders can also be effectively treated with repetitive short-term use of sedative/hypnotics [25].

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, autonomic motor system functioning, behaviors, perceptions, emotions, and 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. Parasomnias are classified based on sleep stage of origin. Recurrent nightmares (the most common of the parasomnias) occur in

15–40 % of normal adolescents. Recurrent, disturbing nightmares are the most common symptom of posttraumatic stress disorder (PTSD). REM behavior disorder (RBD) in which individuals lose the motor block that usually prevents the acting out of dreams 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. 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. This disorder causes an uncontrollable urge to move and to relieve the sensations in the legs. Sleep 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 [26].

The Family Physician and Sleep Medicine

Up to 90 % of adult patients visiting their primary care physician on any given day are experiencing sleep-related symptoms, and at least 1/3 are likely to have OSA. Currently, despite the known increases in morbidity and mortality associated with this diagnosis, only 2–4 % of the individuals likely to have OSA have been tested. Approximately 14 % of the general population suffer from chronic insomnia. Payers, concerned with the potential cost of evaluating and treating this large number of patients, are pushing 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. While sleep medicine consultation for difficult patients is available in many communities, the same standard of care is expected even when diagnosis is limited by screening questionnaires with low sensitivity and efficacy, diagnostic tests with debatable sensitivity, and treatment approaches with limited efficacy.

Currently, few primary care physicians 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. In Queensland and New South Wales, Australia, when family doctors were asked to conduct limited HSTs in their patients with BMI > 30, type 2 diabetes, treated hypertension, and ischemic heart disease, 71 % were found to meet at least minimal criteria for OSA (apnea–hypopnea index (AHI) > 5.0) and 16 % were found to have severe OSA (AHI > 30) [18]. 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 [27].

There are a huge number of patients with sleep-associated diagnoses affecting their mortality and morbidity. The current care system has been able to diagnose and treat OSA for 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 from the sleep laboratory into the primary care office where the HST is beginning to be incorporated becoming a

clinical test as commonly utilized as the EKG and pulmonary function test.

The overwhelming 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 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. These are advantages that the primary care physician has over the specialist in the diagnosis and management of patients with sleep disorders.

Prevention

Sleep disorders are extremely common yet rarely addressed in most primary care practices. A spectrum of poor sleep hygiene practices can contribute to insomnia, especially in high-risk populations such as adolescents and the elderly. Sleep apnea is a primary risk factor for some of the most common chronic illnesses addressed in primary care practice. Due to the significant morbidity and mortality associated with the diagnosis and the difficulty in making the diagnosis using screening tests, the family physician needs to have a high sensitivity to OSA as a potential diagnosis.

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 clearly associated with poor school performance. 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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As part of comprehensive care family physicians are often asked to perform presurgical assessments. Over 50 million procedures are performed yearly, each with varying degrees of risk [1]. These preinterventional assessments weigh the risks inherent in the surgical intervention along with the preexisting medical state of the patient undergoing the proposed procedure. It is necessary to get a whole picture of the patient in order to address these risks and determine if they outweigh the benefits of surgery. One of the most important components of the preoperative evaluation is communication with the surgical team. That is just as important as communicating to the patient how to prepare for surgery and after surgery. This chapter will not address emergency situations, i.e., exploratory laparotomy due to trauma, as they do not always allow enough time for a full assessment which could end up delaying life-saving treatment. It will, however, address the process of preoperative risk stratification. Recommendations derived from current guidelines will be presented to help prevent adverse outcomes such as postoperative deep vein thrombosis.

History

The preoperative medical history serves as the foundation of the preoperative evaluation. The data collected guides the clinician in identifying patient risk factors, which may lead to downstream complications from the planned surgical

Table 1 Risk factors for perioperative adverse events

Glaucoma
Anesthesia complication
Cardiovascular disease
Pulmonary disease
Thromboembolic disease
Coagulopathy
TIA or stroke
Seizure
Blood transfusion
Blood borne infections
Oral history
Functional capacity
Tobacco/alcohol
Steroid use

procedure if not addressed. The preoperative medical history begins with detailing the planned surgical procedure, including listing the referring surgeon's name, procedure type, indication, and date of the procedure. In addition to including a comprehensive past medical and surgical history, the physician must ask about factors which may lead to adverse events during or following surgery (Table 1). For example, the physician must ask about a personal or family history of reaction to anesthesia, such as malignant hyperthermia. Additionally, general anesthesia can trigger acute angle closure glaucoma, so it is important to obtain information about personal history of glaucoma [2].

A complete history of any cardiovascular disease is particularly important in determining the patient's risk for cardiac complications. For individuals with history of chest pain, myocardial infarction, congestive heart failure, or arrhythmia, include relevant test results, treatment plans, and procedures (i.e., stress test, catheterization, and coronary artery bypass grafting). Similarly, history of pulmonary disease such as asthma, chronic obstructive pulmonary disease, and obstructive sleep apnea should include degree of disease severity and management. Any individual with active unstable or severe cardiac or pulmonary disease should be referred for additional testing and consultation prior to proceeding with elective, nonemergent surgery.

History of thromboembolism, such as DVT or PE, and coagulopathy must be clarified prior to surgery as these patients are at increased risk for both hemorrhage and thrombosis in the perioperative and postoperative periods, respectively. The patient's blood type, if known, should also be included, along with any documented history of transfusion reaction.

Even with adoption of universal precautions, a history of blood-borne and other chronic infectious diseases can pose an increased risk to the surgical team. As such, it is important to include history of hepatitis or HIV. Additionally, one must evaluate any recent or current acute infection to ensure that they have resolved prior to the surgery. This is especially important in pediatric, geriatric, and immunosuppressed patients and may require referral to a specialist in severe or complex cases.

A complete list of all prescriptions and over-the-counter medications as well as other supplements and herbal agents should be documented. A plan of action for each of these medications must be developed to inform patients what they can take prior to and after surgery. Particular attention must be given to any significant steroid use over the past 2 years, as these patients are at increased risk of perioperative iatrogenic hypothalamic-pituitary-adrenal axis suppression and may require stress dosing. This will be described in detail later in this chapter. All patients should also be questioned about alcohol, tobacco, and drug use.

The patient's functional status has a major bearing on operative risk. Functional status can be quantified in Metabolic Equivalents of Tasks (MET). One MET is equivalent to the resting metabolic rate. Patients capable of four METs of activity, equivalent to walking four blocks or climbing two flights of stairs, generally have sufficient physiological reserve to tolerate most surgical procedures [3].

Because patients with untreated obstructive sleep apnea (OSA) are at increased risk from surgical procedures, careful attention must be given to identifying undiagnosed or untreated patients. Multiple sleep apnea questionnaires have been developed to help streamline this process; they are generally associated with higher

Table 2 STOP-BANG screening tool for obstructive sleep apnea

S = Snoring. *Do you snore loudly* (*loud enough to be heard through closed doors*)?
T = Tiredness. *Do you often feel tired, fatigued or sleepy during the daytime*?
O = Observed apnea. *Has anyone observed you stop breathing during your sleep*?
P = Pressure. *Do you have or are you being treated for high blood pressure*?
B = BMI >35 kg/m^2
A = Age >50 year
N = Neck circumference >40 cm
G = Male gender

High risk of OSA: ≥3 of the above
Low risk: <3 of the above

sensitivity than specificity aimed at screening for patients who require additional testing. The STOP-BANG questionnaire has been validated to a sensitivity of >90 % when using 3 as the cutoff point (Table 2) [4].

Consider additional workup for patients at high risk of OSA with overnight polysomnography if surgery is not urgent. For patients with known sleep apnea, the clinician should review previous sleep study and document their CPAP or BIPAP settings, type of mask used and oxygen level (if any is being used), as well as their level of adherence.

Physical Examination

A comprehensive physical examination should always be completed starting with the vital signs, and then working in a head-to-toe fashion as usual. For the anesthesiologist, information about a deviated nasal septum, loose teeth, dentures, and the patient's ability to open his or her mouth is relevant to intubation procedures. Tongue and tonsil size and neck circumference, in addition to other nasopharyngeal structures, are also relevant for sleep apnea evaluation. The physician should carefully evaluate the cardiovascular and pulmonary systems. The blood pressure, heart rate, heart rhythm, presence of significant murmurs, and added sounds (particularly an S_3) should be noted. Evaluate for signs of congestive heart failure (rales, jugular venous distension, edema). Assess thoracic expansion and diaphragmatic excursion. Listen for wheezing or rhonchi, which may identify the presence and severity of emphysema, asthma, or chronic obstructive lung disease. As patients with rheumatoid arthritis and Down syndrome are at higher risk of atlantoaxial joint injury during intubation due to underlying instability, test range of motion and consider obtaining cervical spine radiographs. A mini-cognitive examination should be included for all elderly patients prior to surgery, because there is a risk for postanesthesia delirium in this patient population.

Preoperative Testing

Routine laboratory testing in previously healthy patients yields low positive predictive value on the outcome of a surgical intervention [5, 6]. Abnormal laboratory values are not a common cause of canceling or postponing a surgical procedure. Therefore, there are no required "routine" labs before surgery [7]. If laboratory tests are performed they should be tailored to the patient's medical history and physical exam findings. In some instances physicians will decide to order labs during a preoperative evaluation as that may be the only time a patient seeks care.

Despite the evidence listed above, some surgical centers still require a panel of laboratory tests to be completed preoperatively for all patients. For patients with preexisting conditions such as diabetes and renal insufficiency, it makes sense to check current renal function. This can be extended to patients on antihypertensive medications. Complete blood counts should be obtained in patients with a history of anemia and in the elderly. Coagulation tests are important in patients with a history of bruising and/or taking anticoagulation medication. Test all women of reproductive age for pregnancy, as it is unreliable to use results solely from a questionnaire.

Electrocardiograms should not be performed routinely in previously healthy patients undergoing low-risk surgical procedures [6] but should be

done in patients who will have vascular procedures. Patients over the age of 45 should have an ECG performed as there may be a higher change of electrical abnormalities [8, 9]. ECG should also be performed in patients with any prior cardiac history. Test results up to 4 months prior to surgery can be used as there is unlikely to be significant change unless there is a change in the baseline health status of the patient [10].

Assessment

Patient's Preoperative Risk Based on Type of Surgery

One element of the preoperative evaluation is determining the risk level of the surgical intervention being proposed. Not all surgeries carry the same risk of adverse medical outcomes. The family physician should have a general sense of the risk a surgery poses to a patient apart from the patient's own health status. This will be another factor in determining the extensiveness of the evaluation, whether further workup is warranted, and if the surgical intervention is in the best interest of the patient versus no intervention.

Examples of high-risk surgery include vascular, neurosurgery, prolonged surgery, and coronary artery bypass graft surgery. These surgeries carry a reported cardiac risk of greater than or equal to 5 %. Also in this category are trauma and emergency surgeries yet in these situations time does not allow for a full evaluation and benefit tends to outweigh the immediate risk of death without surgery.

Moderate-risk surgeries carry a reported cardiac risk less than or equal to 5 %. These include abdominal surgery, orthopedic, urogynecologic, peripheral vascular surgeries, cancer staging procedures, and prostate surgery as examples. Surgeries with a reported cardiac risk of less than 1 % are considered low risk. Some of them are performed in ambulatory surgical centers ("same day surgery"). Cataract surgery, endoscopy, breast biopsy, podiatry procedures, vasectomy, and appendectomy are examples (Table 3) [11].

Table 3 Surgical procedure risk

High risk (reported cardiac risk ≥5 %)
Coronary artery bypass graft surgery
Pneumonectomy
Trauma surgery
Neurosurgery
Major vascular procedure
Ruptured abdominal viscus
Emergency surgery
Anticipated prolonged surgery, with hemodynamic instability
Moderate risk (reported cardiac risk usually ≤5 %)
Abdominal surgery (open cholecystectomy, colon resection, etc.)
Orthopedic surgery
Urogynecologic surgery (prostatectomy, hysterectomy, cesarean section)
Splenectomy
Peripheral vascular procedures (endarterectomy, femoral-popliteal bypass)
Prostate surgery
Low risk (generally <1 %)
Cataract surgery
Podiatry procedures
Endoscopy and biopsy
Breast biopsy
Mastectomy
Herniorrhaphy
Vasectomy
Appendectomy
Dermatologic procedures

Source: Modified from Eagle et al., with permission [11]

Preoperative Risk Based on Comorbidities

The preoperative risk is even more greatly influenced by a patient's intrinsic risk factors, such as medical comorbidities and low functional capacity. Numerous risk stratification tools have been developed to help assess cardiovascular risk. Of the most widely used indices, the Revised Cardiac Risk Index (RCRI) (Table 4) is a validated tool that incorporates procedural risk with medical comorbidities, including history of ischemic heart disease, heart failure, CVA, diabetes, and renal failure, to generate a level of risk for major cardiac complications from surgery [12].

Table 4 Goldman revised cardiac risk index

Each risk factors is assigned 1 point		
• High-risk surgery (intraperitoneal, intrathoracic, suprainguinal, vascular)		
• History of ischemic heart disease (ECG with pathological Q waves, angina, nitrate use, prior MI, positive stress test)		
• History of heart failure		
• History of CVA or TIA		
• Preoperative insulin use		
• Preoperative serum creatinine >2.0 mg/dl		
# of risk factors	Risk class	% Major cardiac complications (95 % confidence interval)
0	I	0.4 (0.05–1.5)
1	II	0.9 (0.3–2.1)
2	III	6 .6 (3.9–10.3)
3 or more	IV	11 (5.8–18.4)

Patients with an RCRI score of two or more are considered to be at higher risk of postoperative myocardial infarction, pulmonary edema, ventricular fibrillation, or cardiac arrest and should undergo additional cardiac risk stratification.

More recently, the American College of Surgeons National Surgical Quality Improvement (NSQIP) database was utilized to identify five predictors of myocardial infarction or cardiac arrest up to 30 days after surgery: age, type of surgery, functional status, elevated creatinine (>1.5 mg/dl), and American Society of Anesthesiologist class (*Class I*, patient is completely healthy; *Class II*, patient has mild systemic disease; *Class III*, patient has severe systemic disease that is not incapacitating; *Class IV*, patient has incapacitating disease that is a constant threat to life; and *Class V*, a moribund patient who is not expected to live for 24 h, with or without the surgery). These predictors were incorporated into an interactive online risk calculator (http://www.surgicalriskcalculator.com/miorcardiacarrest) for easy point of care use [13]. The NSQIP risk calculator outperformed the RCRI; however, risk for pulmonary edema and complete heart block are not assessed in the former. Therefore, the two provide additive prognostic value which helps guide clinical management [14].

Role of Beta-Blockers in the Perioperative Period

Beta-blockers have been long theorized to be beneficial in the perioperative period in reducing risk of cardiac ischemia through helping to decrease myocardial oxygen demand by slowing the heart rate and prolonging the time for diastolic filling of the heart. However, due to complications from bradycardia and hypotension, such as cerebral ischemia, the routine use of beta-blockers in the perioperative period is not recommended. Patients already taking beta-blockers should continue taking them when undergoing surgery. Additionally, patients who have a high cardiac risk for ischemia (two or more risk factors) and will undergo a high-risk surgery may benefit from being started on a beta-blocker [14]. Available evidence suggests that beta-blockers should be started several days before elective surgery (up to 30 days), with the dose titrated to achieve a resting heart rate of about 60 beats per min [14, 15].

Role of Corticosteroids in the Pre/Perioperative Period

Physiological level of cortisol secreted from the adrenal gland is approximately 8–10 mg/day and increases to approximately 50 mg/day of cortisol during a minor surgery or illness [16]. Patients who are currently taking corticosteroids may be at risk of hypothalamic-pituitary-adrenal axis insufficiency when faced with the stress of surgery. However, recent literature supports that the majority of patients do not need glucocorticoid supplementation. Patients must first be placed in one of three categories dependent on their length and amount of exogenous steroid use: those who do not requiring supplementation, those who do, and those in between the first two categories.

Patients not requiring supplementation include those who have been taking any dose of glucocorticoid for less than 3 weeks [17], those using morning prednisone ≤5 mg/day or its equivalent for any period of time [18], and patients treated with less than 10 mg of prednisone or its equivalent every other day. These patients can safely

continue their glucocorticoid regimen postoperatively. As with all postoperative patients, they should be monitored for hemodynamic stability.

Patients who would benefit from stress dose steroids include those taking 20 mg/day of prednisone or its equivalent for more than 3 weeks [19] and patients on steroids with Cushing's syndrome. Patients taking evening steroid doses or who took doses which could suppress adrenal function within the past year may require further testing (e.g., ACTH stimulation testing, serum cortisol levels, etc.).

If a patient falls under the category of requiring stress dose steroids, the amount of glucocorticoid dosing is dependent on the type of surgery and whether it produces minor or major stress. Minor surgeries or procedures using local anesthetic do not require anything more than the patient taking his/her usual steroid regimen. Moderate surgical stress (e.g., joint replacement) would include in addition to the patient's usual dose intravenous administration of hydrocortisone 50 mg before the procedure and 25 mg every 8 h for 24 h. For major surgical stress (e.g., esophagogastrectomy, total proctocolectomy, open heart surgery), take usual morning steroid dose. Give 100 mg of intravenous hydrocortisone before induction of anesthesia, and 50 mg every 8 h for 24 h. Taper dose by half per day to maintenance level [20, 21].

Sleep Apnea

Patients with sleep apnea are at higher risk of respiratory and cardiac complications and intensive care requirement following surgery involving sedation, analgesics, and anesthesia [22]. A patient's sleep apnea risk can be calculated using one of the various sleep apnea screening tools available, such as the STOP-BANG discussed previously in this chapter. Any patient with a high screening tool score (i.e., STOP-BANG of three or more) should undergo additional testing with overnight polysomnography [4]. Additionally any patient with known sleep apnea that is not following the recommended treatment plan (i.e., CPAP or BiPAP) should also be referred to a sleep specialist prior to surgical clearance [22].

Deep Venous Thrombosis

All surgical patients are at risk for developing deep venous thrombosis (DVT). This risk is increased for elderly patients, the obese, cigarette smokers, cancer patients, patients who are having long procedures, those with previous venous disease, and those with a history of congestive heart failure. The risk of developing a postoperative DVT depends on the type of surgical procedure and the presence of risk factors. The optimal modality for DVT prophylaxis is controversial. Low molecular weight heparin (LMWH), e.g., enoxaparin (40 mg/day or 30 mg q12h), significantly reduces the incidence of DVT and pulmonary embolism in patients undergoing general surgical procedures, such as urological or gynecological surgery, surgery for elective hip or knee replacement or hip fracture, and other orthopedic procedures including trauma surgery. LMWH in doses of 40 mg per day or 30 mg every 12 h significantly reduces the incidence of postoperative DVT [23].

Low molecular weight heparin is expensive and not without side effects (thrombocytopenia, bleeding). Dosing of LMWH must be adjusted according to creatinine clearance for those with known renal insufficiency. Elderly patients should be carefully monitored for bleeding complications. LMWH prophylaxis is not recommended for patients who are to have neurosurgical procedures or spinal anesthesia, because of an increased risk of bleeding that may compromise neurological functioning. Neurosurgical patients or patients undergoing spinal cord surgical procedures should have prophylaxis with intermittent compression or elastic stockings, as there is decreased risk for hemorrhagic complications. A decision to institute pharmacological prophylaxis should be made by the neurosurgeon.

The optimal duration of DVT prophylaxis is controversial. Some would recommend that LMWH or warfarin be continued for 6 weeks to 2 months after surgery. At a minimum DVT prophylaxis should be continued until the patient is ambulatory for functional distances.

Medications

In general, most medications can be continued up to the day of surgery. Monoamine oxidase inhibitors interfere with autonomic function and may cause perioperative hypertension and/or hypotension. These agents may prolong neuromuscular blockade, inhibit hepatic enzymes, and prolong the action of narcotic drugs. If possible, the medication is discontinued a few weeks before surgery. Beta-blockers and clonidine should be continued until the day of surgery, as there is a possibility of postwithdrawal rebound hypertension. The surgeon should order antibiotic prophylaxis, the class depending on the type of surgery and most likely organisms encountered in that region of the body.

Management of anticoagulants may be problematic during the perioperative period. For patients taking warfarin, the risk of discontinuing anticoagulation must be assessed. For patients with metallic heart valves, warfarin discontinuation is risky, although continuing warfarin up to the time of surgery is contraindicated. If it is reasonable to discontinue the warfarin, it is stopped at least 3 days before surgery and then reinstituted after surgery and the patient treated with intravenous heparin. The heparin infusion is stopped 6 h before surgery, and warfarin is reinstituted after surgery. Alternatively, low molecular weight heparin (LMWH) may be used in doses of ~1 mg/h every 12 h adjusted to renal function for 3 days prior to surgery with the last dose administered 12 h prior to the operation. LMWH or warfarin may then be reinstituted after surgery. Aspirin, which irreversibly inhibits cyclooxygenase and affects platelet adhesiveness, should be discontinued 7 days before surgery. Other nonsteroidal and nonsalicylate products may be continued up to surgery.

There is weak evidence to support routine antibiotic prophylaxis for bacterial endocarditis. This is a major update to the 1997 AHA guidelines done in 2007 and again in 2014 [24, 25]. Patients who are at risk for bacterial endocarditis (patients with prosthetic heart valves, previous endocarditis, and congenital cardiac malformations among others) should receive prophylactic antibiotic coverage. Bacterial endocarditis prophylaxis is recommended for cardiac conditions that are high (prosthetic valves) or intermediate risk (mitral valve prolapse with regurgitation), for developing endocarditis, and for procedures that may result in bacteremia.

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Care of the Patient with Sexual Concerns

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Sex, sexuality, and sexual function are often topics that patients want to discuss with their primary care provider [1–4]. The overall prevalence of patients with sexual concerns is estimated at 30 % for men and 30–40 % for women both in the USA and abroad [1–3]. 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 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, 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 (DSM) of Mental Disorders published by the American Psychiatric Association. The newest version of the DSM, the fifth revision (DSM-5 2013), revealed major changes to the definitions of sexual dysfunction [6, 9, 10].

Table 1 Risk factors for sexual dysfunction [1, 2, 5, 6, 13–17, 25]

Age[a] Medical conditions: Atherosclerotic risk factors[a]: Obesity (ED) Diabetes[a] Hypertension Hypercholesterolemia Coronary artery disease[a] Peripheral vascular disease[a] Stroke [a]	Neurologic disease: Degenerative disease[a] Spinal cord injury[a] Parkinson's Dermatologic conditions: Psoriasis Lichen sclerosus Genitourinary disease STI, HIV disease Pain with sex Surgical conditions: Genitourinary[a] Pelvic[a] Spinal[a] Vascular Trauma Injury Psychological: Depression[a] Bipolar Sleep disorders Anxiety Trauma Psychotic disorders	Substance use: Tobacco (ED)[a] Alcoholism[a] Drugs: Cocaine (ED)[a] Marijuana Methamphetamine (ED) Heroin (ED) Anabolic steroids Social interpersonal: Stress: Work Financial Relational Sexual trauma[a] and violence Social-cultural beliefs Religious beliefs Low educational level Unrealistic expectations Influence of media (Internet)	Body image Eating disorder ego-dystonic Sexuality Gender dysphoria Women: Obstetrical complications Postpartum period Breastfeeding Vaginal prolapse PCOS Menopause[a] Men (ED): Pudendal nerve neuropathy long-distance cycling Sedentary lifestyle
Endocrinopathies: Thyroid disorders[a] Hypogonadism[a] Pituitary dysfunction Adrenal dysfunction Hypothalamic dysfunction Rheumatologic disease Chronic renal failure Cirrhosis COPD Cancer treatments: Chemotherapy[a] Radiation[a]			

[a]Causes with a greater prevalence of sexual dysfunction
Condition associated with erectile dysfunction (ED)

Two new categories were developed in the DSM-5: female sexual interest/arousal disorder and genitopelvic pain/penetration disorder. Female sexual interest/arousal disorder in the DSM-5 would have included hypoactive sexual desire and arousal disorders in the DSM-IV-TR. And genitopelvic pain/penetration disorders in the DSM-5 would have included dyspareunia and vaginismus in the DSM-IV-TR. 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 one minute 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 is information 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].

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).

Table 2 Medications with sexual side effects [1, 16, 18, 20, 25–27, 32]

Global sexual dysfunction (SD):	**Women desire only**:	**Men global SD**:
SSRIs[a]`(50 % paroxetine worst)	Trazodone	Ketoconazole
Antiandrogens	Venlafaxine	Spironolactone (gynecomastia)
Women global SD:	Statins	**Erectile dysfunction**
TCAs	Beta-blockers	Antipsychotics[a]
Barbiturates	Spironolactone	Antidepressants[a]
Lithium[a]	Methyldopa	Venlafaxine
Affect desire and arousal:	Danazol	Benzodiazepines
Benzodiazepines	GnRH agonists	Beta-blockers[a]
Clonidine	Contraceptives	Thiazide diuretics
Tamoxifen	Histamine 2 blockers	Opiates
GnRH analogues	Promotility agents	Antiretroviral
Ultralight contraceptive pills	Indomethacin	Histamine 2 blockers (cimetidine)
Aromatase inhibitors	Ketoconazole	TCA
Chemotherapeutic agents	Phenytoin	Phenytoin
Affect desire and orgasm:	**Arousal only**:	Phenobarbital
Antipsychotics[a]	Anticholinergics	Lithium
Amphetamines	Antihistamines	Bromocriptine
Narcotics		Levodopa
Digoxin		Gemfibrozil
		Methotrexate
		5-Alpha reductase inhibitors
		Corticosteroids

[a]Most commonly has sexual side effects

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) risk and/or contraceptive management as appropriate depending on the patient's needs [1, 3, 12].

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, 5, 14].

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 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, 5, 8, 14].

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, 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, 5, 12, 14, 15, 17].

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, trauma/surgical repair such as episiotomy repair, and STIs. The clitoris should be inspected for abnormalities, included tethering as seen in lichen sclerosus [4]. A speculum and bimanual exam may reveal a 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]. 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 rectal exam should be used to assess for tone and in men for any signs of prostatic disease [2, 5, 8, 12, 15].

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 hemoglobinA1c, 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, 5, 12, 15, 17].

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) v. acquired (secondary) and situational v. 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, 5]. The typical pattern of a psychosocial cause is a younger patient with acute onset of symptoms in a specific situation with intermittent symptoms and decreased desire with absent or minimal underlying medical conditions [2, 5].

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 hypoactive sexual desire with delayed orgasm and anorgasmia [1, 2, 5, 12, 14, 17].

The DSM-5 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).

Table 3 Medical treatment of sexual dysfunction in women [1, 14, 16, 20, 28, 29]

Female sexual interest/ arousal disorder	1. Postmenopausal women and post-oopherectomy with desire disorder: testosterone (not FDA approved in women), studies show 300 mcg/day patch. Studies show consistent improvement and least side effects at 300 mcgs. 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-month trial. Measure baseline testosterone and after 3–6 weeks of initial treatment. If ongoing, check levels q 6 months. If no benefit at 6 months, discontinue. There is no efficacy and safety data after 24 months. Recommend initial evaluation with endocrinology or OB/GYN as off-label use and comanagement. Suggest monitoring liver function and lipids. Intrinsa 300 mcg/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 dose mild), cv risk (risk not established)
	2. Postmenopausal women with vaginal atrophy can be treated with vaginal estrogen (tablets, gels, cream, and rings equally effective) and sexual lubricants. 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
	3. Small studies with women with both arousal and desire disorders showed improvement of genital sensation and satisfaction with foreplay and intercourse with sildenafil (Viagra) 25–100 mg daily
Female orgasmic disorder	1. Testosterone for hypogonadism. Doses above
	2. Add bupropion SR 150–300 mg daily (higher dose better)
	3. Phosphodiesterase inhibitors (PDE5I) limited studies and mixed results and most no improvement. One small study showed improvement in orgasmic dysfunction in women on SSRIs and sildenafil
Genitopelvic 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)

Treating Sexual Dysfunction: General Principles

The well-person 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. Also it is important to emphasize the breadth of a person's sexuality, like normalizing masturbation and in some cases same-sex attraction [1, 8, 12, 14, 16, 17, 19].

In patients diagnosed with sexual dysfunction, it is important to address habits such as tobacco use, excessive alcohol use, and illicit drug use as they are well known to contribute to sexual dysfunction [12, 14, 15, 18]. Poor sleep due to an underlying physical or mental health issue affects multiple areas of functioning as does stress at work or in the patients relationship [1, 12, 14, 15, 17]. Being overweight can affect body image and obesity is associated with erectile dysfunction [12, 15, 18]. Patients should be encouraged to be physically active, as exercise is associated with increased sex drive and better sexual functioning [12, 15, 18].

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 may be 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].

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 interpersonal violence in past or current relationships

Table 4 Treatment of sexual dysfunction in men [8, 12, 15, 17–19, 23, 24, 30]

Male hypoactive sexual desire disorder	Testosterone for hypogonadism: depo-testosterone (T) 200–250 mg every two weeks
	Transdermal testosterone (closer to circadian levels)
	Patch applied to the arm, back, or upper buttocks alternate sites and avoid sun-exposed area as 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. [a]In T replacement monitor CBC, LFTS, PSA
	Bupropion 150 mg–300 mg daily
Premature ejaculation	SSRIs
	Fluoxetine (Prozac) 20–40 mg/day
	Citalopram (Celexa) 20–40 mg/day
	Paroxetine (Paxil) 10–40 mg/day[a] 20 mg on demand 3–4 h before sex
	Sertraline (Zoloft) 50–200 mg/day[a] 50 mg on demand 4–8 h before sex
	Tricyclic antidepressants (TCAs)
	Clomipramine 12.5–50 mg daily[a] 25 mg on demand 4–24 h before sex
Delayed ejaculation	Almost always related to underlying cause. Also includes retrograde ejaculation
ED: first line	Phosphodiesterase inhibitors (PDE5I) (see Table 4) [a] require 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 with comanagement with urologist. Needs plastic ring around penis and scrotum to maintain erection. Ring should not be in place for more than 30 minutes. 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
	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

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 and sexual function and reduce anxiety associated with sexual (dys) function. Couples therapy can explore specific concerns in the relationship, such as communication issues. Sex therapy can explore the dynamics in the relationship or in the individuals that is 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].

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 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]. There is a paucity of high-quality research on medical treatments for sexual dysfunction in women. There is more research on sexual dysfunction in men, specifically erectile dysfunction [1, 14, 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 sexual activity in almost all or all sexual encounters, and/or minimal arousal or sensations genitally or otherwise with sexual activity [9].

In younger women, 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 release and reuptake inhibitors (SSRIs) and oral contraception pills (OCPs) [14]. As women 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]. In postmenopausal women, vaginal atrophy and lubrication issues are common (see Table 3 for treatment details) [1, 14]. Education about masturbation is important. Using adjunctive aids, such as the Eros clitoral device, which is FDA approved, can improve arousal through direct stimulation [1, 14, 20]. Transdermal testosterone is the most studied hormone replacement 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 [14, 21, 28]. Bupropion has been shown to improve symptoms of sexual functioning in women; higher doses show better response. However, the studies have small numbers of patients and inconsistent methodologies [1, 14, 21]. In postmenopausal women diagnosed with both interest and arousal disorders, there is a small study that showed women had improved genital sensation and satisfaction with foreplay or intercourse with sildenafil (Viagra) [1, 21]. (see Table 3 for dosing and more detail).

In women with **orgasmic disorder**, most or all of the patient's sexual activity must either have 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 direct masturbation and sexual positions that focus on maximize clitoral stimulation (coital alignment) [1, 14, 16]. Medications include bupropion as a possibility for improvement of anorgasmia, although there are few studies with small sample sizes [1, 14] (see Table 3 for more detail).

Women with **genitopelvic 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, postsurgical/obstetrical complications, bladder, uterine, ovarian, and intestinal disease) [14]. And consider other etiologies, such as

Table 5 Phosphodiesterase inhibitors (PDE5I) [15, 18, 30]

PDE5I	Dosing	Side effects
Sildenafil (Viagra) Short acting: Tmax 1 h, ½ life 4 h	Range 25–100 mg/dose Starting dose 50 mg Take ½–4 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, ½ 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 ½–4 h(s) before sex	Class effects QT prolongation[a] High-fat meal can delay absorption Use lower dose if managing side effects from other medications
Tadalafil (Cialis) Long acting: Tmax 2 h, ½ 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 ½–12 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 **Contraindicated with nitrate therapy*****	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	HIV protease inhibitor 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 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[a] Acute myocardial infarctions no nitro 24–48 h if on PDE5I**

vaginal atrophy or neuropathy [1, 14]. Behavioral techniques include non-penetrating pleasuring techniques and biofeedback [1, 14].

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). In both vulvodynia and vaginismus, a referral to a specialized physical therapist maybe helpful [1, 14, 22]. Ospemifene (Osphena) is a new selective estrogen receptor modulator (SERM), which has been FDA approved for moderate to severe dyspareunia secondary to vulvar and vaginal atrophy in postmenopausal women. Efficacy data is limited [31].

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]. 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 one minute 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 [22, 24]. Delayed ejaculation is most often associated with medication side effects and substances, such as SSRIs [9] (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]. 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]. 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]. In addition, questions about nocturnal erections, AM erections, and quality of erections with masturbation are important when distinguishing between a psychosocial etiology and an underlying organic cause [12, 18].

Phosphodiesterase inhibitors (PDE5I) are first-line therapy for ED. They are most effective in the cases of antidepressant side effects, diabetes mellitus, and spinal cord injury [12, 15, 18]. 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 [15]. If patients with ED are identified as having hypogonadism, they should be supplemented with testosterone and Initially comanaged with an endocrinologist (see Tables 4 and 5 for details of treatment). Surgical options are considered last resort [12, 18].

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, 21]. Hypogonadism can be a cause of erectile dysfunction as well as hypoactive arousal disorder. 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 comanaged with an endocrinologist. Bupropion may improve symptoms of sexual functioning and desire in men as in women [1, 17, 18].

In **premature ejaculation,** ask the patient if they ejaculate within 1 min of vaginal penetration most or all the time and if this is before the patient would have liked to ejaculate (i.e., 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 [9]. 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, 19].

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 [8, 19]. Condoms can decrease sensitivity [8, 19].

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 [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 [19]. Both the International Society of Sexual Medicine and the AUA have evidence-based guidelines with slightly different dosing. The AUA recommends men under 18 and those with a history of bipolar disorder not be prescribed these medications [8, 23, 24]. Some smaller studies are suggesting that combination of SSRIs and PDE5Is may be a recommended treatment in the future [24]. There is limited evidence that surgical procedures work for premature ejaculation [8, 23, 24].

PDE5s can be used in premature ejaculation with signs of erectile dysfunction as first-line therapy according to the ISSM. There is conflicting evidence about the use of PDE5I in men with normal erectile dysfunction, as well as concerns about priapism [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 with delayed ejaculation or absence of ejaculation, and 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). There is little research that provides high-quality evidence about treatments for sexual dysfunction secondary to antidepressants. In men, the recommendation is to use PDE5Is and in women the addition of bupropion (300 mg) at higher doses is the most studied. 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 or mirtazapine) [1, 14, 27, 32].

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, 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 comanaged or referred depending on provider comfort and patient preference [2, 8, 18].

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Family Medicine
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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.

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 contributes to the development 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 have an AUD [2]. The risk of alcohol dependence is 12.5 % over a patient's lifetime [3].

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 [4].

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 [5].

Screening

The United Stated Preventative 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 [6]. For patients between the ages of 12–17 the USPSTF believes the evidence is insufficient to assess the balance of benefits and harms of screening by a primary care physician.

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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 society. Because there is no safe level of alcohol consumption during pregnancy, abstinence is recommended.

The USPSTF recommends three tools for screening adults for alcohol misuse in the primary care setting; the Alcohol Use Disorders Identification Test (AUDIT) available at http://www.integration.samhsa.gov/AUDIT_screener_for_alcohol.pdf, the abbreviated AUDIT-Consumption (AUDIT-C) and the single-question method. 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.

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 (four or more for women) is considered high risk for excessive and problematic alcohol use.

The Single-question 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.

The CAGE questionnaire can be used for adolescents and adults. 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 [4]. The questions are: 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?

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 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.

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Table 1 Definition of alcohol use disorder [52]

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

Treatment of Alcohol Use Disorder

The physician's attitude toward the patient is an important aspect of AUD treatment. Alcoholism is a particularly stigmatized mental disorder [7]. These patients provoke more social rejection and negative emotions and are deemed responsible for their condition [7].

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 physician 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 [8]. 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 [9] (Fig. 1). Patients who drink despite brief interventions are candidates for intensive therapy.

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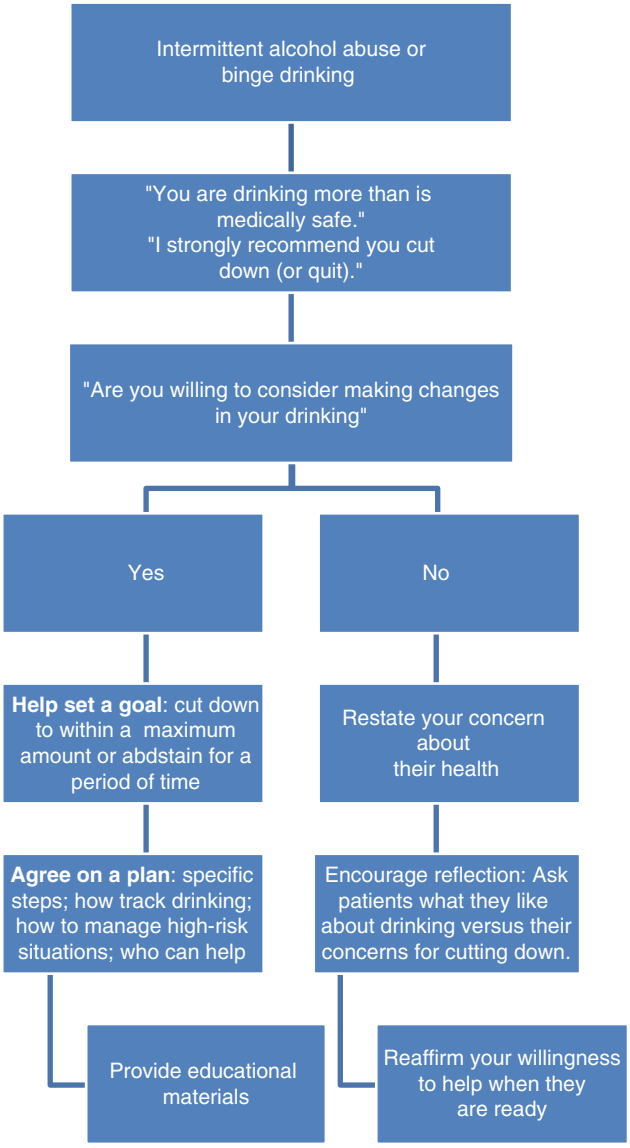

Fig. 1 Brief intervention for intermittent alcohol abuse or bing drinking http://pubs.niaaa.nih.gov/publications/Practitioner/CliniciansGuide2005/clinicians_guide7.htm#top

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) (See "Long-Term Management of Alcohol Dependence"). The time and location of the local AA meetings can be found during the patient's encounter and the patient encouraged to attend a meeting that day.

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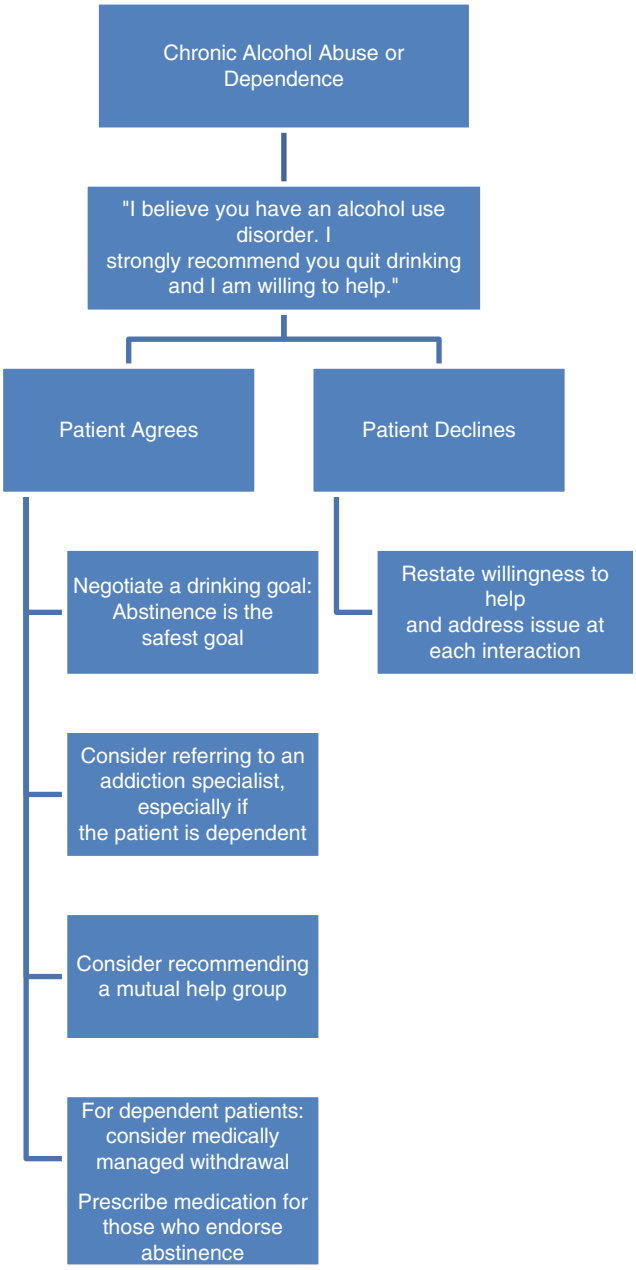

Fig. 2 Confronting chronic alcohol abuse or dependence http://pubs.niaaa.nih.gov/publications/Practitioner/CliniciansGuide2005/clinicians_guide7.htm#top

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 [3]. The symptoms begin 6–24 h after the last alcohol intake or a significant reduction in alcohol intake [10].

Alcohol withdrawal involves the central nervous system, autonomic nervous system, and cognitive function [11]. 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;

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or (8) tonic-clonic seizures [10]. 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 [10].

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 [12].

AWS severity is assessed using a validated instrument. The instrument often recommended is the Clinical Institute Withdrawal Assessment – A revised (CIWA-Ar) available at http://www.mdcalc.com/ciwa-ar-for-alcohol-withdrawal/ [13]. 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 [3]. 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 [14]. A SAWS score <12 is mild AWS and ≥12 is moderate AWS.

Treatment of AWS

The AWS treatment goals are to reduce withdrawal symptoms, prevent complications (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 [10]. 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.

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 [10]. 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), lack of a support network [10].

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 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 [11]. The dispensing of medication requires clinical judgment and creates issues of control, thus caregivers must be informed of their role and be in agreement [10]. 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.

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Inpatient Treatment of AWS

AWS patients could 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 experience AWS. When patients are admitted they become accessible to health care professionals for an intervention [15]. 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 [16]. For the nondependent patient, alcohol consumption was reduced if they had more than one brief intervention during their hospital stay [17]. A single screening and brief intervention in the Emergency Room or nonemergency Department hospital setting did not reduce alcohol consumption [18].

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 [10]. Most patients are given medication, particularly if there is any question about their duration of abstinence.

Because AWS patients are often nutritionally depleted, thiamine and folic acid supplementation are given to all patients. Thiamine 100 mg once a day is recommended to reduce the risk of Wernicke's encephalopathy (oculomotor dysfunction, abnormal mentation, and ataxia). Folic acid 1 mg daily is recommended. 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 [19]. They should be administered early in the AWS course. No evidence supports the superiority of any medication in treating AWS.

BZDs can be long-acting (chlordiazepoxide, diazepam) or intermediate-acting (lorzepam, oxazepam). Long-acting BZD may be more efficacious in preventing delirium [20]. They have active metabolites that prolong their sedative and anxiolytic effects [20]. Experts contend that long-acting BZDs provide a smoother withdrawal experience with fewer fluctuations in symptoms; however, intermediate-acting BZD have been used successfully [19]. In patients with hepatic dysfunction, the intermediate-acting agents may be safer because they have no active metabolites. Chlordiazepoxide or oxazepam have 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 them in small amounts.

Carbamazepine and valproic acid are effective in treating AWS [21]. However, anticonvulsant medication efficacy data is limited and carbamazepine is associated with dizziness, ataxia, diplopia, nausea, and vomiting [22]. Limited evidence supports the use of valproic acid over BZD [23]. Oxcarbazepine was as effective as carbamazepine in treating AWS [24], although one placebo-controlled randomized trial did not support that contention [25]. Gabapentin was effective in treating AWS and reducing drinking during withdrawal [26]. 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 [27]. As adjunctive therapy, beta-blockers and the alpha-adrenergic agonist clonidine are effective in reducing adrenergic symptoms but are not effective in preventing

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Table 2 Medications used to treat AWS

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

withdrawal seizures [19]. Neither phenothiazines nor barbiturates are recommended for AWS treatment in the outpatient setting [19]. Phenytoin is not effective in the treatment or prevention of withdrawal seizures [11].

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. The fixed-dose schedule utilizes a specific dosage at specific intervals regardless of the patient's symptoms. Additional medication is given if needed to control symptoms and the dosage reduced if overmedication occurs [10].

The symptom-triggered schedule utilizes medication when the patient has significant symptoms (CIWA-Ar $>$ 9; SAWS $\geq$ 12). This schedule reduced medication use and shortened duration of treatment for inpatients [28]. 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 [29]. 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. However, for the hospitalized patient a loading-dose of a long-acting BZD has been found to improve outcomes in AWS [30]. 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.

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Table 3 Fixed dosage and symptom-triggered dosage options to treat AWS [10]

Treatment day	Fixed dosage schedule (orally)	Symptom-triggered schedule (orally) For SAWS $\geq$ 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

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 $\leq$8 or SAWS is $<$12, medication can be reduced and eventually discontinued. Alcohol withdrawal symptoms should resolve within 7 days of abstinence. 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 usually 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.

Management of DTs

DTs, severe AWS, is associated with an increased risk of death. DTs symptoms begin about 3 days after initial withdrawal symptoms develop [31]. DTs risk factors include sustained heavy drinking, age over 30, more days since last drink, and, most importantly, a prior episode of DTs [10]. Hallucinations, common in DTs and primarily visual, are not dangerous but are distressing to the patient and his or her caregiver.

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) [3]. 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.

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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, propofol (0.3–1.25 mg/kg/h IV) can be administered in the ICU [3]. Another ICU medication is dexmedetomidine (Precedex®) (0.4–0.7 mcg/kg/h IV), an α_2-adrenergic agonist has been administered [32]. Intravenous fluids should be utilized to maintain hydration and to treat electrolyte abnormalities [31].

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 [33]. The American Society of Addiction Medicine's Patient Placement Criteria (Second Edition) can assist clinicians in determining appropriate levels of care. Levels of care include residential programs, partial hospital programs, intensive outpatient programs, and outpatient care [34].

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 [34].

Therapeutic communities provide comprehensive care and emphasize graduated personal and social responsibility. Appropriate patients tend to be relapse prone, polysubstance abusers, often with psychiatric comorbidities and poor social support. Staff and clients reside together and interact in activities with the goals of assimilation of social norms, development of social skills, and positive impact upon attitudes, perceptions, and behaviors. Typically, stays have ranged from 18 to 24 months with a desired minimum of 90 days.

Oxford House (www.oxfordhouse.org) is a publically 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 [34].

Intensive Outpatient Programs (IOP's) 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 [34]. **Outpatient care** model utilizes similar services as IOP's but interventions are less frequent (less than 10 h/week) and shorter in duration [34].

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 [35]. The 12 steps serve as a template for behavioral interventions aimed at maintenance of sobriety and the

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fellowship provides an abstinent social network to replace lost "drinking buddies" [36]. Daily meetings are offered in wide variety of venues and group composition varies by age, gender, and interests of the participants. Common elements include the acknowledgement 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 [36–38]. However, a Cochrane review concluded there is a lack of experimental evidence supporting the effectiveness of 12-step programs for alcohol dependence [39].

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 [36].

Individual therapy occurs in sessions typically lasting 30–60 min. The frequency and duration of such sessions is 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 [36].

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 [40].

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 [41].

Motivational Enhancement Therapy (MET) is based on the premise that responsibility and capacity for change lies 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 [36].

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. **Couples-Based Therapy** engages the client's spouse 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 [42].

Pharmacologic Interventions

Less than 10 % of patients with AUD receive medications to assist in maintaining sobriety [43]. Three medications are approved by the Food and Drug Administration for the treatment of alcohol dependence: Naltrexone (oral and injectable), acamprosate, and disulfiram [43, 44]. Acamprosate and oral naltrexone

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are effective in reducing a return to drinking, although no studies demonstrate superiority of one over the other [43] (Table 4).

Naltrexone

Naltrexone, available in oral (*ReVia*) and injectable formulation, has proven efficacy in reduction of alcohol consumption. 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 [43]. 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. Adverse effects are similar to the oral formulation with the addition of injection site reactions and interstitial or eosinophilic pneumonia [19].

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. However, the *COMBINE* study comparing the efficacy of acamprosate, naltrexone, and placebo found acamprosate to be no more effective than placebo. Though well tolerated, common side effects include, diarrhea, insomnia, anxiety, depression, nausea, and dizziness [43].

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 [43]. 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 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 [45].

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 [43]. 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 [43].

Gabapentin (*Neurontin*) has proven efficacy in dosages of 900 or 1800 mg daily versus placebo. Side effects are dizziness and sedation which are dose-dependent [46]. Results were mixed in clinical trials comparing Baclofen 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 [47]. Selective serotonin reuptake inhibitors (SSRIs) have been found to be effective in the management of alcohol dependence in patients with a comorbid depression diagnosis [48].

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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 LFT's 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 LFT's 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 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
Selective serotonin reuptake inhibitors	Various	No	Serotonin mediated	Depends upon drug chosen	Use in comorbid depression More effective in late onset alcoholism

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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 LFT's 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 LFT's 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 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

(*continued*)

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Table 5 (continued)

Medication	Dose	FDA indication/	Mechanism of action	Side Effects	Cost	Caveats
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
Selective serotonin reuptake inhibitors	Various	No	Serotonin mediated	Depends upon drug chosen		Use in comorbid depression More effective in late onset alcoholism
Odansetron	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

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 [49].

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 [50].

Intervention for sleep disturbances may benefit patients in maintaining sobriety as some patients use alcohol for its sedative effects. Promotion 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. Though some research of Internet- and telephone-based models have proven benefit, further adequately-powered randomized-controlled trials are needed to determine the efficacy of these interventions. Additionally, how these interventions can best be

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incorporated into a comprehensive continuing care model for the long-term management of alcoholism must be explored [51].

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Family Medicine
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Care of the Patient Who Misuses Drugs

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According to the 2013 National Survey on Drug Use and Health (NSDUH), an estimated 24.6 million Americans aged 12 or older were current illicit drug users [1]. This represents nearly 10 % of the population aged 12 and older, and primary care providers encounter these patients on a regular basis. Unfortunately, primary care physicians may not feel well prepared to deal with substance abuse due to lack of training, discomfort with the subject, time constraints, and lack of confidence in available treatments [2]. However, patients with substance use disorder can be well cared for using a chronic disease framework that is familiar to most primary care providers.

General Guidelines

The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) no longer separates substance abuse and dependence but groups them together on the continuum of substance use disorder [3]. Patients can be described as having a substance use disorder if they fulfill at least 2 of 11 criteria (Table 1). The disorder can be classified as mild (2–3 criteria), moderate (4–5 criteria), or severe (6 or more criteria). Importantly, patients who are on long-term opioid treatment will likely experience pharmacologic dependence but would not necessarily be considered to have a substance use disorder.

For most patients, substance use disorders are chronic. Unfortunately they are often treated as acute illnesses, but there is evidence that using a chronic disease model may improve outcomes [4]. Screening for substance use, making the diagnosis, offering brief interventions, providing medication management, and knowing when to refer are the essential elements of chronic disease care and apply well to substance use disorders. While referral to addiction specialty services is often indicated, primary care physicians with adequate training and support can offer many of these services for patients.

Screening

The US Preventive Services Task Force has determined that there is insufficient evidence to recommend screening for substance use disorders [5]. Despite the lack of evidence, the American Academy of Family Physicians and the American Psychiatric Association recommend incorporating substance use screening into primary care [6]. The Screening, Brief Intervention, and Referral to Treatment (SBIRT) model is a comprehensive approach that can be used to identify patients with substance use disorders, offering tailored interventions as well as appropriate referrals [7]. The screening tools that are most often used and have been validated for use in primary care are the Drug Abuse Screening Test-10 (DAST-10) and the single-question screening test [8].

The National Institute on Drug Abuse (NIDA) recommends using the single-question screening tool [9]. The single-question screen has a sensitivity for substance abuse disorder of 90–100 % and a

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Table 1 Substance use disorder criteria [3]

1. Impaired control
Taking more of the substance that was intended
Inability to cut back or stop using
Spending excessive time obtaining, using or recovering from substance use
Cravings for the substance
2. Social impairment
Failure to fulfill obligations due to use
Recurrent use despite negative consequences to interpersonal relationships
Reducing or eliminating meaningful social activities due to use
3. Risky behavior
Recurrent use in physically dangerous situations
Continued use despite negative physical or psychological consequences caused by the substance
4. Pharmacologic indicators
Tolerance – increasing the amount of substance to reach the desired effect
Withdrawal – physiologic responses to decreasing or stopping the drug

Table 2 Single-question screen [10]

How many times in the past year have you used an illegal drug or used a prescription medication for nonmedical reasons?
A positive response is at least once

Table 3 CAGE questionnaire

1. Have you ever felt you should *c*ut down on your drinking?
2. Do people ever *a*nnoy you by criticizing your drinking?
3. Have you ever felt *g*uilty about your drinking?
4. Have you ever had a drink first thing in the morning? *E*ye opener

specificity of 74 % [10]. NIDA offers a helpful screening algorithm (www.drugabuse.gov/sites/default/files/pdf/screening_qr.pdf) (Table 2).

Medical professionals often use the CAGE questionnaire to screen for alcohol abuse. CAGE has high test-retest reliability, and it is a valid tool for identifying alcohol abuse in many different settings [11]. CAGE is short and easy to use but is limited in identifying less severe alcohol problems and cannot detect any other form of substance use [11] (Table 3).

Brief Intervention

Brief interventions and counseling patients with substance use disorders can follow the same guidelines as counseling patients with diabetes or other chronic illnesses. Motivational interviewing can be key to approaching patients in a nonjudgmental manner (Table 4). Evidence for brief interventions in an outpatient setting is conflicting. Brief interventions have been shown to decrease drug use [12]. However, the ASPIRE trial failed to show that brief interventions decreased drug use in patients who were identified by screening [13].

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Table 4 Motivational interviewing principles for physicians

Principle/technique	*Rationale*
Resist the righting reflex	Physicians want patients to change or correct unhealthy behaviors. Telling them to do so is a natural reflex, but it can generate resistance in patients. Instead, help them generate their own argument for healthy changes
Understand the patient's motivations	Patients are more likely to change for reasons that they value highly. By eliciting these reasons, physicians can be more effective
Listen to the patient	Physicians need to listen to patients to elicit the best path to behavior change
Empower the patient	Physicians can help patients take an active role in their health care and support self-efficacy
Elicit-provide-elicit	A nonconfrontational approach to advice or information giving that allows the patient to express his or her feelings about change and assists the physician in assessing readiness for change
Decision analysis ("pros and cons")	Physicians can help patients make changes by articulating the advantages and disadvantages of the changes
Reflections	Physicians can identify statements that the patient makes in support of change and reflect them back to the patient, highlighting the patient's reasons for change
Affirmations	Most patients with substance abuse and dependence feel guilt and shame about their drug use, and may lack confidence that they can make changes. Physicians can promote self-efficacy with honest and meaningful affirmations
Less effective approach	*More effective approach*
Physician: "You need to stop using cocaine. It's damaging your heart" Patient: "I don't think it's the cocaine. My friends use cocaine too, and they don't have heart problems"	Physician: "How does it feel when you hear that cocaine may be causing your chest pain?" Patient: "I don't know what to think about it, but it's got me thinking"
Physician: "Now that you are pregnant, you need to stop abusing pain pills for your developing baby" Patient: "I'll do the best I can"	Physician: "Is there anything about your use of pain pills that you are concerned about?" Patient: "Yes, my husband told me he would leave me if I started taking pain pills again"
Physician: "I'm going to refer you to a special program for people with addiction to pain pills" Patient: "I told you already, drug treatment isn't for me"	Physician: "We talked a little about some possible treatment options, but I'm interested in hearing what you think would work for you" Patient: "I won't go to drug treatment, but if there is a medicine I could take that would help me stop, I would do that. Also I used to go to NA, and that seemed to help"
Patient: "I almost didn't come in to see you. I just can't stop using cocaine" Physician: "Did you go to the NA meetings and see a therapist like we discussed?"	Patient: "I almost didn't come in to see you. I just can't stop using cocaine" Physician: "Quitting cocaine is difficult for most people, and I've been impressed by how hard you have worked to cut back"
Physician: "Using cocaine can cause heart attacks. You are putting yourself at risk each time you use, and you need to stop"	**Elicit knowledge and opinions:** Physician: "What do you know about how cocaine affects your health?" Patient: "Well, some people get holes in their noses, but I don't use that much, so I don't think it's affecting me" **Provide tailored information and advice:** Physician: "I'm glad you haven't used enough to have that problem. You might be surprised to know that even small amounts of cocaine increase your risk of heart attack, stroke, and high blood pressure. Sometimes people have heart attacks from using cocaine just one time" **Elicit response and feelings:** Physician: "How does that new information strike you?" Patient: "I don't know. I guess it might be more dangerous than I thought"

(*continued*)

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Table 4 (continued)

Principle/technique	*Rationale*
Physician: "Don't you see that your cocaine use is hurting your whole family?" Patient: "What do you know about my family?"	Physician: "What do you like about using cocaine?" Patient: "It lets me forget all the things that are bothering me, and it gives me energy to get things done" Physician: "And what do you not like about cocaine use? What makes you think about stopping?" Patient: "I don't want my kids to see me high, and it's definitely starting to get in the way of work. I'll have to stop someday or it will be hard to keep this job"
Patient: "I don't want to be using cocaine when I'm 80. That would be crazy" Physician: "So why don't you stop?" Patient: "I'm just not ready yet, OK?"	Patient: "I don't want to be using cocaine when I'm 80. That would be crazy" Physician: "You want to stop using cocaine someday" Patient: "Yes, I do. I guess the question is when"
Patient: "I can't believe I relapsed again. It's so frustrating" Physician: "You've just got to get up and try again"	Patient: "I can't believe I relapsed again. It's so frustrating" Physician: "You're frustrated, but the fact that you came back to talk about it tells me that you're determined. You've quit before, and I'm confident you can do it again"

Stimulants: Cocaine and Amphetamines

Cocaine is the second most commonly used illicit substance (marijuana is first) [14]. Although use of cocaine declined during the early 1980s, its misuse increased dramatically in 1985 with the marketing of "crack" cocaine. Crack is a highly addictive form of cocaine readily accessible at a low cost (as inexpensive as $10–$25). Crack cocaine has changed cocaine from a drug of the rich and affluent to a drug anyone can afford (including adolescents and children). In 2013 NSDUH estimated that there were 1.5 million current cocaine users age 12 or older [1] which has declined since the 1990s and early 2000s. However, it is estimated that every day approximately 1,600 Americans try cocaine for the first time [1]. A gram of cocaine typically costs $60–$80 and is almost always "cut" or diluted with lactose, levamisole, mannitol, cornstarch, or other similar substance. Adulterants make up over 50 % of the total volume of cocaine sold [15].

Cocaine hydrochloride is water soluble and can be injected intravenously or inhaled intranasally ("snorted"). Cocaine hydrochloride cannot be smoked because it decomposes. If it is dissolved in ether and distilled, the base form of cocaine (freebase) is reprecipitated, and this substance can be smoked. "Crack" cocaine is produced by dissolving cocaine hydrochloride in sodium bicarbonate and distilling off the water. It then forms "rocks," which can be smoked. The term *crack* comes from the noise the rocks make as they are heated and smoked.

The physiologic effects of amphetamines (including methamphetamine and dextroamphetamine) are very similar to cocaine. However, the "high" from cocaine lasts less than an hour, while amphetamines can last several hours [16]. Amphetamine pills can be crushed and snorted, dissolved in water and injected, or smoked. Pure methamphetamine ("ice" or "glass") is most often smoked in a glass pipe which allows the user to experience immediate effects without the risks of injecting [16]. *Crack* and *crank* are two street terms that are commonly confused. Crank is a street name for methamphetamine that can be taken as pills, injected, or snorted. Crack is freebase cocaine.

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When prescription stimulants are abused, it is often by crushing and snorting or mixing with water and then injecting. Methylphenidate (Ritalin, Adderall) causes a response similar to cocaine when injected. Both substances cause an immediate increase in dopamine, producing the "high" experienced by users.

Effects

Cocaine causes euphoria, talkativeness, increased energy, and increased confidence. The immediate euphoria is quickly followed by a letdown characterized by depression, irritability, restlessness, and a generalized feeling of uneasiness and discomfort. When users start feeling letdown, they use more cocaine, which results in blood levels that cause medical complications and can be lethal. Frequent presenting complaints for patients using cocaine include chest pain, cardiac arrhythmias, new onset seizures, anxiety, chronic sinusitis, headaches, and weight loss. Physical findings suggestive of cocaine use include agitation, dehydration, malnutrition, tachycardia, elevated blood pressure, rhinorrhea, cough, wheeze, and poor dentition.

Agitation is the most common presenting symptom of amphetamine misuse. Hallucinations, suicidal ideation, delusions, and confusion may be present. Cardiac symptoms include chest pain, palpitations, and myocardial infarction. Acute signs of amphetamine intoxication include an elevation in the blood pressure and pulse, dilated pupils, tremor, cardiac arrhythmias, and increased reflexes. The long-term effects of amphetamine abuse include impaired concentration, abrupt mood changes, weight loss, paranoid delusions, and violence.

Acute Medical Treatment

The three primary cardiovascular complications of cocaine abuse are hypertension, myocardial ischemia, and cardiac arrhythmias. Cardiac toxicity can occur with all three routes of administration (intranasal, intravenous, and inhaled). In individuals who are sensitive to cocaine or who have coronary artery disease, cardiac symptoms can occur with relatively low doses of cocaine.

Chest pain is the most common medical problem related to cocaine, but unfortunately it can be difficult to distinguish chest pain from ischemia and myocardial infarction [15, 17]. Patients who present with cocaine-associated chest pain may also have diaphoresis and shortness of breath, but these are not predictive of ischemia [17]. Electrocardiographic (ECG) changes of ischemia are common, but occasionally are not present even with an acute myocardial infarction caused by cocaine. One group estimated that the sensitivity of ECG changes for identifying myocardial infarction was 35 % [17]. It is impossible to clinically differentiate patients with cocaine-induced chest pain and those experiencing a myocardial infarction [17]. In addition, it has been shown that the Thrombolysis in Myocardial Infarction (TIMI) risk score is not clinically useful in this population [17]. Due to the challenges of identifying ischemia in cocaine users, it has been suggested that patients who present with cocaine-associated chest pain who have a normal ECG and negative cardiac biomarkers be observed and followed with serial ECG and troponins [17]. Cocaine misuse should be suspected in any patient under 50 years old who presents with chest pain [15].

Up to 6 % of patients presenting with cocaine-induced chest pain will progress to infarction [17]. The risk of an acute myocardial infarction increases in chronic users but can happen after the initial use as well. During the initial 60 min after cocaine use, the relative risk of myocardial infarction increases almost 24-fold [15]. Even cocaine users who are asymptomatic have been found to have significant myocardial damage [15].

All patients presenting with cocaine-associated chest pain should be treated with aspirin. Both benzodiazepines and nitroglycerine have been shown to relieve chest pain symptoms, although more study is needed to determine if these medications affect cardiovascular outcomes [17]. Historically beta blockers have been avoided in cocaine-associated chest pain due to a fear of inducing unopposed vasoconstriction. While beta blockers are still to be avoided, retrospective studies have not shown an increase in adverse outcomes in patients who were given beta blockers and subsequently had positive cocaine testing [17]. Patients who present with cocaine-associated myocardial infarction should receive

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nitroglycerine, calcium channel blockers, and fibrinolytics when applicable [17]. It is important to note that these recommendations are based on expert opinion due to lack of data [17].

The most common arrhythmia associated with cocaine misuse is tachycardia, but it usually resolves spontaneously as the drug is metabolized or with use of an anxiolytic agent.

Smoking cocaine can cause a cough with black sputum production and dyspnea. Hemoptysis and spontaneous pneumothorax are common in crack addicts. Pulmonary edema (noncardiac) may be an acute hypersensitivity reaction. Asthma can be exacerbated by smoking crack cocaine. Pollutants in crack can also cause bronchitis and tracheitis.

Seizures are common with cocaine misuse. Cocaine decreases the seizure threshold and increases the body temperature, which makes an individual more susceptible to seizures. Intravenous benzodiazepines are the treatment of choice for seizures caused by cocaine.

Serious obstetric complications, including placental abruption, preterm birth, and preeclampsia, are increased in pregnant women who use cocaine [18]. Cocaine easily crosses the placental barrier, and intrauterine exposure can cause fetal demise, growth restriction, and congenital malformations [18]. Newborn infants may demonstrate signs of cocaine withdrawal, including irritability, tremulousness, and poor eating. Women who use cocaine and are pregnant or may become pregnant should be counseled about the potential risks of cocaine use and offered addiction treatment options.

The most common cocaine-induced psychiatric disorders are paranoid delusions and hallucinations which can occur in up to 50 % of cocaine users [19]. Hallucinations called “snow lights” (flashing visual hallucinations) and “coke bugs” (tactile and visual hallucinations) are common with cocaine misuse.

Patients experience withdrawal symptoms when they stop using cocaine. Depression is common after cocaine cessation, and patients frequently experience severe anhedonia that may last several months (antidepressants may help).

Almost all patients who snort cocaine have chronic sinusitis. They may have unilateral inflammation of the nose (cocaine addicts frequently snort in one nostril at a time so only one nostril is inflamed). Chronic rhinitis, perforations of the nasal septum, and abscessed teeth are common in cocaine snorters. Patients who misuse cocaine frequently engage in high-risk sexual behaviors that expose them to sexually transmitted diseases and human immunodeficiency virus (HIV) disease.

Treatment of Addiction/Dependence

Very few pharmacologic interventions have been shown to improve abstinence rates in cocaine users [20]. Current research does not support the use of anticonvulsants, antidepressants including SSRIs, antipsychotics, or dopamine agonists for the treatment of cocaine dependence [20, 21]. There is some limited evidence supporting the use of bupropion, dexamphetamine, and disulfiram as treatment options; however, these require more study before being recommended as therapies used in primary care for cocaine dependence [20].

Opioids

Opioids include both natural opiates such as opium and morphine as well as derivatives and synthetic opioids like heroin and oxycodone. According to the National Survey on Drug Use and Health, 4.8 million Americans have used heroin [1]. In 2011, heroin use was involved in 83 emergency department (ED) visits per 100,000 people [22]. While this number has not changed significantly over the last 10 years, the number of ED visits involving prescription opioids has increased by 153 % over the same time period [22]. In 2013, 4.5 million Americans were considered current users of prescription pain medications for nonmedical reasons [1]. Opioid overdose deaths are also on the rise [23].

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Opioid addiction often begins with taking prescription opioid pills, progresses to crushing the pills to snort or inject, and ends with injecting heroin [24]. The cost of a single dose of heroin varies depending on the location and purity but generally ranges from $10–25. Heroin is often less expensive than buying pills; however, tolerance builds quickly to opioids, and an addict can often spend more than $1200 a month obtaining heroin [25]. In 2006 Americans spent $11 billion on heroin [25].

Opioid pain medications can be crushed to snort or inject although manufacturers are continually developing new ways to prevent this abuse. Heroin is often bought and sold as a white or brown powder that can be snorted, smoked, or injected.

Effects

Initially, opioid users experience euphoria as well as warm flushing and clouded mental thinking. This "rush" is more pronounced with injecting versus other methods. Afterward the user becomes very drowsy which is often referred to as going "on the nod" [26].

Opioids in general can cause shallow breathing, constipation, pruritus, sedation, and nausea. The presenting signs and symptoms of opioid overdose are stupor, miosis, hypotension, bradycardia, and decreased bowel sounds. Frequently needle marks or tracks are present if drugs are being injected. In more severe cases, respiratory depression with apnea and pulmonary edema can occur.

Acute Medical Treatment

Naloxone (Narcan) is the primary treatment for opioid overdose in addition to oxygen supplementation [27]. As a full opioid antagonist, naloxone will reverse all effects of opioids including respiratory depression and analgesic effects. An initial dose of 0.4–0.8 mg can be given intravenously, intramuscularly, or subcutaneously and repeated every 2–3 min up to a total dose of 10 mg. The goal in treatment is to reverse the respiratory depression, not to get the patient awake and alert, which may precipitate an acute withdrawal syndrome. Intravenous naloxone acts almost immediately and will take effect within 1–2 min. The effects of naloxone last between 45 and 90 min and doses often need to be repeated depending on the initial opioid [27]. The effects of heroin can last up to 5 h.

Naloxone has been prescribed for overdose prevention to heroin users and more recently to patients on high-dose opioid pain medications [28]. Auto-injection devices are available (Evzio) as well as intranasal devices (generic).

Opioid withdrawal is not life-threatening although it is very uncomfortable. Symptoms can be managed with clonidine 0.1–0.2 mg orally every 6 h or clonidine transdermal patch 0.1 mg weekly, although the patient should be monitored for hypotension [29]. Benzodiazepines should not be used to control symptoms during opioid withdrawal [30].

Treatment of Dependence/Abuse

Treatment options for opioid dependence include detoxification (withdrawal), agonist maintenance therapy, or antagonist therapy. Detoxification can occur in an outpatient or inpatient treatment facility. For many patients, maintenance therapy with either methadone or buprenorphine is more successful than tapering or detoxification [31, 32].

Medication maintenance therapy can include methadone or buprenorphine. Buprenorphine is often combined with naloxone when used for maintenance therapy (Suboxone, Zubsolv). According to a Cochrane review, buprenorphine in fixed doses of at least 7 mg daily performed as well as fixed doses of methadone in retaining patients in treatment and suppressing illicit opioid use [33].

Methadone treatment for opioid dependence is only available through a regulated Opioid Treatment Program (methadone treatment facility). However, buprenorphine/naloxone can be prescribed in any setting as long as the physician obtains further education and a special licensure from the

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DEA. Prescribing buprenorphine/naloxone in a primary care setting may help improve the health of this underserved population. Primary care physicians are well equipped to provide routine preventative services, targeted screening (HIV, HCV), and chronic illness management. In fact, integrating buprenorphine maintenance treatment in a federally qualified health center has been shown to engage this vulnerable population with primary care, improve health outcomes, and increase preventative services completed [34]. More information can be found at http://buprenorphine.samhsa.gov.

Pregnant women who are opioid dependent may be maintained during pregnancy on methadone or buprenorphine. There is no strong evidence that one medication should be used over the other [35, 36]. In order to avoid neonatal abstinence syndrome, motivated women can slowly taper off opioids during their late second or third trimester without increasing the risk of pregnancy complications [36]. However, it is generally advised that women stay on maintenance medication due to risk of relapse after tapering [35].

The final option for opioid dependence treatment is antagonist therapy with naltrexone (Revia, Vivitrol). Naltrexone is a full opioid antagonist similar to naloxone. Both drugs undergo extensive first-pass metabolism. Naltrexone metabolizes into an active metabolite and can be given orally (Revia) or as a monthly injection (Vivitrol). Naloxone metabolizes into an inactive metabolite and thus is only given as an injection or intranasally for opioid overdose (see above). For highly motivated patients, extended-release injectable naltrexone (Vivitrol) may be a reasonable treatment option [37].

Marijuana

Marijuana is the most commonly used illicit drug in the United States [38]. The National Survey on Drug Use and Health found that 19.8 million people in the United States had used marijuana in the past month [1]. Given the recent legalization and decriminalization of marijuana across the country, this number may increase. In addition, emergency room visits involving the use of synthetic cannabinoids (K2, Spice) have doubled from 2010 to 2011 [39]. Marijuana use can cause dependence and addiction although at lesser rates than other drugs of abuse. Approximately 9 % of marijuana users become dependent as opposed to 15 % of those who try cocaine and 24 % of those who try heroin [40]. This number may seem small, but because the total number of people who try marijuana is much greater than those who try cocaine, the prevalence of marijuana dependence is twice to that of cocaine [40].

Marijuana can be smoked as a cigarette (joint) or through a pipe or bowl (bong). Hashish is a more concentrated form of marijuana that is either pressed into a solid or used as a resin which can be smoked or ingested. Hemp is a low-THC variety of cannabis that is grown to make rope or clothing. The high from marijuana is caused by the activation of cannabinoid receptors by the main active chemical in marijuana, THC (tetrahydrocannabinol). This activation works in the same way as almost all drugs of abuse and activates the reward pathways by releasing dopamine. Users typically feel an initial euphoria followed by sedation [38]. However, some users also experience anxiety and paranoia. Marijuana may be "laced" with other drugs, such as cocaine, phencyclidine (PCP), or other hallucinogens, causing bizarre reactions. Marijuana is highly lipophilic, with a half-life of approximately 3 days. Long-term users can expect daily cough, sexual dysfunction, and loss of motivation [38].

The most common physical signs of marijuana misuse are tachycardia and conjunctival irritation (which may be masked in experienced users by using eye drops). Urine testing is the most effective laboratory method for screening patients suspected of marijuana misuse. In daily misusers, urine toxicology screens may remain positive for several weeks. After a single misuse episode, the urine test is positive for 3–4 days.

Treatment for marijuana dependence typically consists of cognitive behavioral therapy and motivational enhancement therapy [40]. Marijuana withdrawal syndrome is similar to nicotine withdrawal, and

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patients experience irritability, sleep disturbances, and depression [40]. Most pharmacotherapy research has targeted the withdrawal symptoms with the most promising therapy being synthetic THC [40].

1. Effects
2. Acute medical treatment
3. Treatment of addiction/dependence

Hypnotics and Anxiolytics

Both hypnotics and anxiolytics are commonly prescribed in primary care practices. Hypnotics are medications prescribed for insomnia and include zolpidem and zaleplon (Ambien and Sonata). Anxiolytics typically refer to benzodiazepines (BZDs). BZDs can be short acting (alprazolam, lorazepam) or long acting (clonazepam, diazepam). From 1969 to 1982, diazepam was the most commonly prescribed drug in the United States [41]. However, since that time, the prolific prescribing of BZDs has been called into question given the high rate of abuse, dependence, and adverse events associated with this class of medications. Short-term use of BZDs is known to impair learning and memory as well as increase the risk of accidents and injuries [41]. Long-term use is less well studied but has also been associated with cognitive decline and may be a risk factor for dementia [41, 42]. The sedative effects of hypnotics and BZDs are increased when used in combination with alcohol or other sedatives. In fact, as much as 80 % of unintentional overdose deaths that involve opioids also involve BZDs [43]. Concomitant prescription of opioids and BZDs is common, and opioid abusers will often use BZDs to prolong and enhance the opioid high [41, 43].

Withdrawal can occur after just 6–8 weeks of chronic use of BZD or hypnotics [44]. In addition, many patients will experience rebound of their original symptoms when stopping BZDs [45]. Mild withdrawal symptoms can include anxiety and nightmares and severe withdrawal can be life-threatening (see Table 5). In order to avoid withdrawal, BZDs should be slowly tapered over 2–4 months. For chronic users, tapering can be accomplished by decreasing the dose by 10 % per week [44]. Cognitive behavioral therapy has been shown to assist patients who are discontinuing BZDs [44]. Care should be taken not to prescribe BZDs or hypnotics to patients with a history of BZD abuse as the risk of relapse is high. These patients should also be cautioned against alcohol use.

Hallucinogens

Hallucinogens are defined as drugs that produce visual, auditory, tactile, and in some cases olfactory hallucinations. Lysergic acid diethylamide (LSD) is the most potent, most common hallucinogen. It is referred to as acid, dots, cubes, window pane, or blotter. LSD can cause bizarre behavior that begins within an hour after ingestion, peaks in about 3–4 h, and lasts up to 12 h. Tolerance develops quickly to LSD and users must increase their dosage to have the same effect. Hallucinogens are particularly dangerous because their effects are highly unpredictable. Paranoia, depression, anxiety, acute psychosis, combative behavior, and panic attacks are associated with “bad trips.” On physical examination, patients have pronounced pupillary dilation, tachycardia, sweating, and fever. Death can result from cardiovascular compromise due to hypertension or can be self-inflicted due to impaired judgment [19]. Patients diagnosed with LSD intoxication need to be carefully screened for other problems such as hypoglycemia, head trauma, drug withdrawal, electrolyte abnormalities, endocrine disease, central nervous system (CNS) infection, hypoxia, and toxic reactions to other street or prescription drugs. The preferred treatment

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Table 5 BZD withdrawal symptoms [41, 45]

Mild	Severe
Irritability	Delirium tremens
Panic attacks	Psychosis
Sleep disturbance	Mania
Dry heaves and nausea	Attempted suicide
Sweating	Convulsions
Headache	Catatonia
Muscle aches	

for an acute intoxication is "talking down" the patient whereby patients are reassured that their symptoms are drug induced and they will resolve [19]. In severe cases, haloperidol or a benzodiazepine can be used [19]. Patients may have chronic effects from LSD that include flashbacks, psychoses, depressive reactions, and chronic personality changes. Other hallucinogens include MDMA (ecstasy, molly), mescaline (from peyote cactus), and psilocybin (from some mushrooms).

Physical dependence does not develop to hallucinogens. In addition, psychological dependence is rare likely due to the lack of reliable euphoria [19].

Inhalants

Up to 20 % of children in middle school and high school have misused inhaled substances [46]. The popularity of inhalants in this age group is likely because they are easy to obtain legally and very inexpensive. Frequently abused inhalants include gasoline, airplane glue, aerosol whipped cream, cleaning agents, Freon, rubber cement, and lighter fluid. At a low dose, inhaling these agents can cause euphoria, light-headedness, and a state of excitation. At higher doses, users can experience fearfulness and auditory and visual hallucinations [19]. Users may also exhibit nystagmus, nausea and vomiting, abdominal pain, and psychomotor retardation [19]. Inhalants are sniffed, "bagged" (inhaling the substance from a plastic or paper bag), and "huffed" (inhaling the vapors by holding a piece of cloth soaked in the volatile substance against the mouth and nose).

Inhalants are rapidly absorbed into the bloodstream, are highly lipid soluble, and produce central nervous system depression. Tolerance can develop although withdrawal is typically mild [19]. In the emergency room, solvent misuse frequently can be mistaken for acute psychiatric problems because of the altered mental state and hallucinations. Death can result from respiratory depression, cardiac arrhythmias, or asphyxiation. Chronic abuse may cause brain atrophy, permanent hepatic and renal damage, and bone marrow toxicity [19].

Signs of inhalant abuse include stains on clothing, unexplained burns, and the odor of solvents on the patient's clothing or breath [19]. Supportive care for acute inhalant toxicity usually allows symptoms to clear within 4–6 h and cardiac monitoring is often necessary.

Tobacco and alcohol use are discussed in other chapters.

Patients in Recovery

Little has been written about the care of patients after they recover from drug or alcohol addiction. Because many medical problems resolve as patients abstain from illicit drugs and alcohol, it is reasonable to wait a few months before treating less severe medical problems. Patients in recovery should be asked

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about their continued abstinence from drugs and alcohol. If family members are present, ask them how the patient is doing. Positive support of patients, even if they have relapsed, is imperative.

Any medication has the potential to cause a relapse, especially mood-altering medications. Prescription medications can cause a relapse by lowering patients' resistance or by patients becoming addicted to the prescribed medication. The following guidelines are for patients with a history of substance use disorder: [47]

1. Whenever possible, use nonpharmacologic treatments. Encourage patients to exercise, meditate, and change their diet; use acupuncture or biofeedback before prescribing medications.
2. Avoid benzodiazepines and narcotics.
3. Be cautious about prescribing "cue stimuli" medications, such as inhalants in former intranasal cocaine addicts.
4. Choose medications with side effects that may be beneficial, such as beta-blocking drugs to treat hypertension because they decrease anxiety, which is common during early recovery.
5. Beware of increased drug sensitivity secondary to damage caused by patients' previous drug and alcohol misuse. Patients need a thorough evaluation focusing on specific complications from their previous addiction. Injection drug users must be assessed for hepatitis and HIV disease.
6. Before prescribing medications, wait for normal resolution of medical problems associated with withdrawal and early recovery, such as hypertension, depression, hyperglycemia, and tachycardia.
7. Anticipate the normal changes (insomnia, anxiety, depression, and some sexual dysfunction) that occur during recovery and counsel patients about them so the patients are less likely to be concerned or to seek medications (Tables 6 and 7).

Table 6 Resources for patients and providers (adapted from [6])

Resource	Description	Appropriate referrals
Alcoholics Anonymous: aa.org Dual Recovery Anonymous: draonline.org SMART Recovery: smartrecovery.org Women for Sobriety: womenforsobriety.org	Free group sessions that are led by a peer and typically based on a 12-step model	Any patient with past or current substance abuse
Inpatient detoxification (medically supervised withdrawal)	Intensive, onsite care where patients are continuously monitored and treated throughout their withdrawal, sometimes for days or weeks	Patients who experience a serious withdrawal syndrome or have significant psychiatric comorbidities
Outpatient detoxification	May include counseling sessions, pharmacologic management	Stable patients without serious withdrawal
Residential treatment	Structured, monitored live-in program that may last for several months	Patients with more severe addictions, significant comorbidities who are in need of a safe living environment or at high risk of relapse
Maintenance treatment	Typically for opioid addiction. Methadone or buprenorphine prescribed by licensed providers in the outpatient setting	Patients with opioid dependence who are relatively stable but have high risk of relapse

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Table 7 Find a provider

American Society of Addiction Medicine Physician Finder (http://community.asam.org/search/default.asp?m=basic)
Buprenorphine Physician and Treatment Program Locator (http://buprenorphine.samhsa.gov/bwns_locator)
SAMHSA Behavioral Health Treatment Locator (http://www.findtreatment.samhsa.gov)

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Care of the Patient with Chronic Pain

Kelly Bossenbroek Fedoriw

Contents

Definition and Scope of Chronic Pain

Chronic pain is pain that persists beyond the typical healing time of 3–6 months. The Institute of Medicine estimates that 100 million people in the United States suffer from chronic noncancer pain (CNCP) which is more than the number of people with diabetes, coronary heart disease, stroke, and cancer combined [1]. The annual health care costs for patients with CNCP are estimated at $635 billion (in 2010 dollars), but despite the high prevalence, CNCP remains undertreated [2].

Paralleling the incidence of CNCP, prescriptions for opioid pain medications have skyrocketed over the past 15 years, with approximately 259 million opioid prescriptions written by providers in 2012 [3]. This increase in prescriptions has been associated with an alarming increase in accidental overdose deaths involving prescription opioids but shown to have little impact on effectively reducing pain [3, 2].

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.

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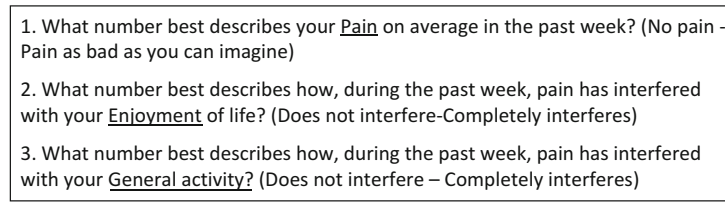

Fig. 1 Pain, enjoyment, and general activity (Scale 1–10) [7]

Treating Acute Pain

Acute pain tends to have an easily identifiable cause and typically resolves when the inciting injury heals. Nonopioid medications should be considered first line for acute pain [4]. However, when 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. The transition from acute pain to chronic pain is not always obvious. 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.

Patient Assessment

Every patient in pain requires a thorough initial history and physical exam to assess pain characteristics including location, intensity, quality, duration, and relieving and exacerbating factors. Previous investigations and treatments tried will help guide treatment options and social history; substance use history and any psychiatric comorbidities need to be explored as well [5, 6]. Categorizing the type of chronic pain will help determine possible treatment options.

A functional assessment is essential for patients in chronic pain [6]. Tools for use in primary care include the Pain, Enjoyment, and General Activity questionnaire (see Fig. 1) and the Physical Functional Ability Questionnaire by the Institute for Clinical Systems Improvement. The goal of therapy for chronic pain is to improve function and quality of life as well as control pain. Patients should be aware of these goals, and function should be tracked over time.

In addition to assessing the patient, providers must set expectations for pain management at the first visit. Chronic pain by definition is a chronic disease and must be managed similarly to other chronic diseases. Many patients will require multiple modalities, self-management skills, and more than one medication trial to achieve improvement in their function.

Types of Pain and Treatment Options

Pain can be 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 system. Importantly, the categories are not mutually exclusive, and patients can be affected by both types of pain. However, classification of mechanism for a given patient can be helpful in guiding therapy [5].

Inflammatory pain – Arthritis, surgery, and infection are potential causes of inflammatory pain. Hallmarks 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 and not medication [5]. 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 [5]. 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) [5]. Neuropathic pain is less responsive to opioid analgesics [8]. Treatment options for neuropathic pain are numerous and can be divided into two categories: disease-specific treatments such as improved glucose control for diabetic neuropathy or surgery for nerve decompression and symptom management. First-line treatment options for symptom management include anticonvulsants, tricyclic antidepressants (TCAs), and serotonin-norepinephrine reuptake inhibitors (SNRIs) [5].

Chronic Pain Treatment Algorithm

See Refs. [5, 6, 8] (Fig. 3, Table 1)

Muscle Relaxants

Little evidence exists to support the use of muscle relaxants such as cyclobenzaprine (Flexeril) and tizanidine (Zanaflex) for chronic low back pain [5, 9]. Carisoprodol (Soma) is structurally similar to alprazolam, has little utility in the management of chronic pain and can be habit forming [5]. If used chronically, muscle relaxants cause central relaxation and may carry the risk of physical dependence [9]. Baclofen is a commonly used antispasmodic agent which may improve neuropathic pain and may be less habit forming than muscle relaxants [9, 5].

Multiple Modalities

Treatment plans for chronic noncancer pain must include more than just medications. Exercise therapy is recommended for chronic low back pain as well as other types of chronic pain and can reduce functional limitations [5]. Patients with CNCP are often deconditioned due to inactivity, and providers should recommend gradually increasing general activity levels as well as formal exercise [5]. In addition, massage has been shown to reduce for chronic pain due to low back pain, knee osteoarthritis, and fibromyalgia [5].

Psychotherapy is an additional 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 [11]. 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 Fig. 2).

Surgical interventions are sometimes warranted but are beyond the scope of this chapter (Table 2).

Opioid Trial Algorithm

See Refs. [4–6, 12, 13] (Fig. 4)

Indications/Contraindications and Risks of Opioids

Guidelines have been developed to help clinicians safely and effectively treat CNCP with opioids [6, 13–15]. However, many of the recommendations are based on limited data. Most trials involving CNCP are short (<3 months) and evaluate pain scores and not patient function [14]. While the

Table 1 Selected analgesics [8–10]

Drug name	Usual dose	Maximum dose	Comments
Acetaminophen (Tylenol, others)	500–1,000 mg po q6-8 h	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
NSAID			
Ibuprofen (Motrin, others)	400–800 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: 1. Elevated blood pressure 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 or SR–75 mg po q12h	200 mg/day	
Ketoralac (Toradol, others)	10 mg po q4–6 h	40 mg/day	
	Pts <65 years: 30 mg IM/IV q6h	120 mg/day	
	Pts ≥65 years: 15 mg IM/IV q6h	60 mg/day 60 mg/day	
Diclofenac (Cataflam, Voltaren)	50 mg po q8h or SR-75 mg po q12h	200 mg/day	
Meloxicam (Mobic)	7.5–15 mg daily	15 mg/day	May be more selective for COX-2 at low dose (7.5 mg)
Nabumetone (Relafen)	500–750 mg po q8-12 h	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 Less effective treatment for acute pain
TCA			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, 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
Nortriptyline (Pamelor)	10–100 mg qHS	300 mg/day	
Desipramine (Norpramin)	50–150 mg daily	150 mg/day	
SNRI			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)	50 mg po BID	200 mg/day	
Duloxetine (Cymbalta)	60 mg daily	60 mg/day	Specifically approved for diabetic neuropathy, fibromyalgia, chronic low back pain. No known cardiovascular risk. Nausea is a common side effect
Anticonvulsant			Typically used for neuropathic pain and chronic headaches. Can be added to TCA. Similar efficacy to TCA

(*continued*)

Table 1 (continued)

Drug name	Usual dose	Maximum dose	Comments
Gabapentin (Neurontin)	600–1,200 mg TID	3,600 mg/day	Start at 100–300 mg qHS and titrate to effective dose. Common side effects include dizziness, fatigue, impaired concentration, and peripheral edema. Reduce dose in renal impairment
Pregabalin (Lyrica)	75–300 mg po BID	600 mg/day	FDA approved for fibromyalgia. May have anxiolytic benefits
Carbamazepine (Tegretol)	200–400 mg BID	1,200 mg/day	Effective for trigeminal neuralgia, painful diabetic neuropathy and postherpetic neuralgia
Oxcarbazepine (Trileptal)	300–600 mg po BID	1,200 mg/day	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 use
Diclofenac (Voltaren gel)	2–4g topical q6-8 h	32 g/day	Topical NSAID with low risk of systemic side effects

OTC over the counter, *COX* cyclooxygenase, *NSAID* nonsteroidal antiinflammatory drug, *SR* sustained release, *TCA* tricyclic antidepressant, *SNRI* serotonin-norepinephrine reuptake inhibitor

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

Do not let pain dictate activity or appointments. Schedule regular visits and medications at regular intervals instead of as needed

Fig. 2 Cognitive behavioral techniques [5]

risk of overdose death with high-dose opioids has been well established, there are no high-quality controlled trials that evaluate the effectiveness of opioid therapy for longer than 1 year [14].

There is no evidence in favor of one opioid over another for the treatment of CNCP [14, 15]. Opioid selection is primarily based on cost, side effects, and patient comorbidities. Specifically, there is no compelling evidence to prescribe a long-acting medication accompanied by a short-acting medication for "break-through pain" [15]. Patients who are well controlled and functional on a short-acting medication four times a day do not necessarily need the addition of a long-acting medication.

Methadone deserves specific mention due to the unique risks associated with chronic methadone use [16]. Methadone should be a medication of last resort given the significant risk of QTc prolongation and long, variable half-life which can make titration difficult. Patients who require a trial of methadone can be started at 2.5 mg orally every 8 h. Dosage increases should occur no more frequently than once a week [15]. The starting dose of methadone, even in a patient on high doses of other opioids, should not be higher than 30–40 mg per day [15]. The QTc interval should be monitored with electrocardiograms prior to starting methadone, after 1 month, and yearly while therapy continues. Providers should avoid the use of other medications that prolong QTc and increase monitoring if necessary. Methadone should not be used to treat break-through pain or on an as-needed basis [15].

Given the well-established risks of opioids high-dose therapy, in particular, should be reconsidered. Not surprisingly, limiting dosage is associated with decreased number of overdose deaths [13]. Multiple guidelines support opioid dosage limits, but there is inconsistency over specific threshold recommendations [14]. Patients who do not experience a response to low-dose opioids (up to 40 mg morphine equivalent dose (MED)) or moderate doses (40–90 mg MED) are unlikely to respond to higher doses [13]. Patients

Table 2 Selected opioid analgesics [8, 9]

Drug name	Usual adult starting dose	Duration of action	Comments
Don't use Meperidine (Demerol) due to toxic metabolite			
Many opioids are available in multiple formulations: immediate release, sustained release or extended release formulations. This will affect the starting dosage as well as the dosing interval			
Codeine	15–60 mg po q4h	4 h	Avoid in children
Fentanyl (Duragesic)	Depends on previous opioid dosage[a]	72 h/patch	Warn patients that exposing the patch to heat can increase release of fentanyl and increase risk of respiratory depression Keep away from children. Exposure to patch can be fatal CYP3A4 inhibitors (eg ketoconazole, clarithromycin) can dangerously increase serum fentanyl levels
Hydrocodone (Norco)	5–10 mg po q4-6 h	4 h	
Hydromorphone (Dilaudid)	2 mg po q6-8 h	4–6 h	
Methadone (Dolophine)	2.5–10 mg po q8-12 h	8–12 h	Monitor the initial titration period carefully as the half-life is variable (up to 5 days). Serious arrhythmias can occur and are dose dependent
Morphine (MS Contin)	10–30 mg po q4h (IR)	4 h (IR)	Use with caution in patients with renal impairment.
	15–30 mg po q8-12 h (ER)	8-12 h (ER)	
Oxycodone (Roxicodone, Oxycontin)	5–15 mg po q4-6 h (IR)	4–6 h (IR)	1.5 times as potent as oral morphine
	10 mg po q12 (ER)	12 h (ER)	
Oxymorphone (Opana)	5–15 mg po q4-6 h (IR) 10 mg po q12 (ER)	4–6 h (IR) 12 h (ER)	3 times as potent as oral morphine
Tapentadol (Nucynta)	50–100 mg po q4-6 h (IR) 50 mg po q12 (ER)	4–6 h (IR) 12 h (ER)	Less potent than morphine but fewer GI side effects
Tramadol (Ultram)	50–100 mg po q4-6 h (IR) 100 mg po q24 (ER)	4–6 h (IR) 24 h (ER)	Maximum dose is 400 mg/day (IR) and 300 mg/day (ER)

OTC over the counter, COX cyclooxygenase, NSAID nonsteroidal antiinflammatory drug, SR sustained release, TCA tricyclic antidepressant, IR immediate release, ER extended release
[a]Not recommended for opioid naïve patients

requiring high doses (>100 mg MED) should be re-evaluated for the cause of their pain, and providers should consider more frequent monitoring, evaluation of adherence to the treatment plan, and consider referral to pain specialists [13, 15].

Mitigating Risks

In addition to establishing a diagnosis, patients should be stratified according to risk. Mitigating the hazards of opioid misuse and addiction requires routine and ongoing risk assessment. Multiple patient screening tools are available,

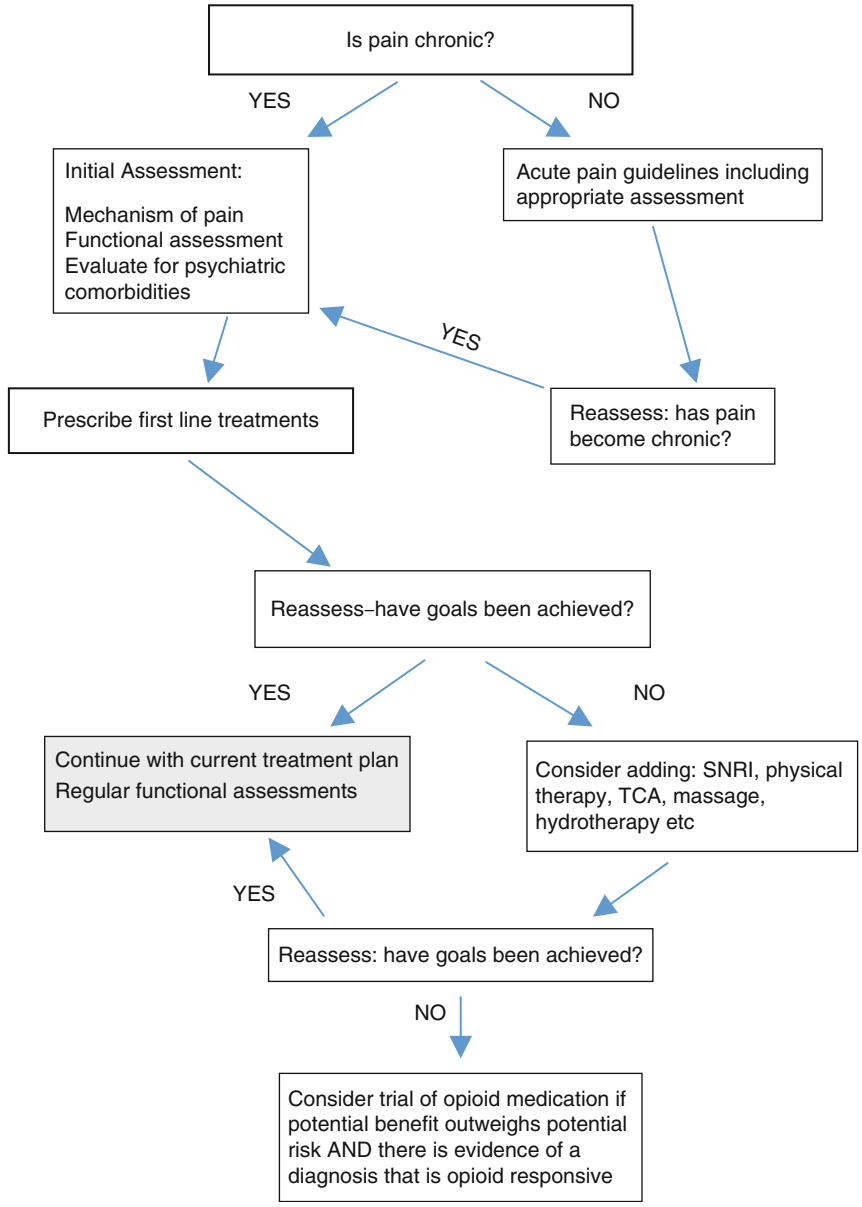

Fig. 3 *SNRI*, Serotonin-norepinephrine reuptake inhibitor, *TCA*, Tricyclic Antidepressant

but unfortunately the effectiveness of these tools is not well studied [14]. However, this should not preclude screening patients. Tools that are often used include the Opioid Risk Tool, Addiction Behaviors Checklist, and the Screener and Opioid Assessment for Patients with Pain [6]. Categorizing patients into high, moderate, or low risk groups can help guide management. High-risk patients and those with significant psychiatric comorbidities or history of drug abuse should be managed only by providers experienced with this population, and comanagement with psychiatry or an addiction specialist is strzongly recommended [15].

Patients must give informed consent prior to starting an opioid trial. Providers should plan for

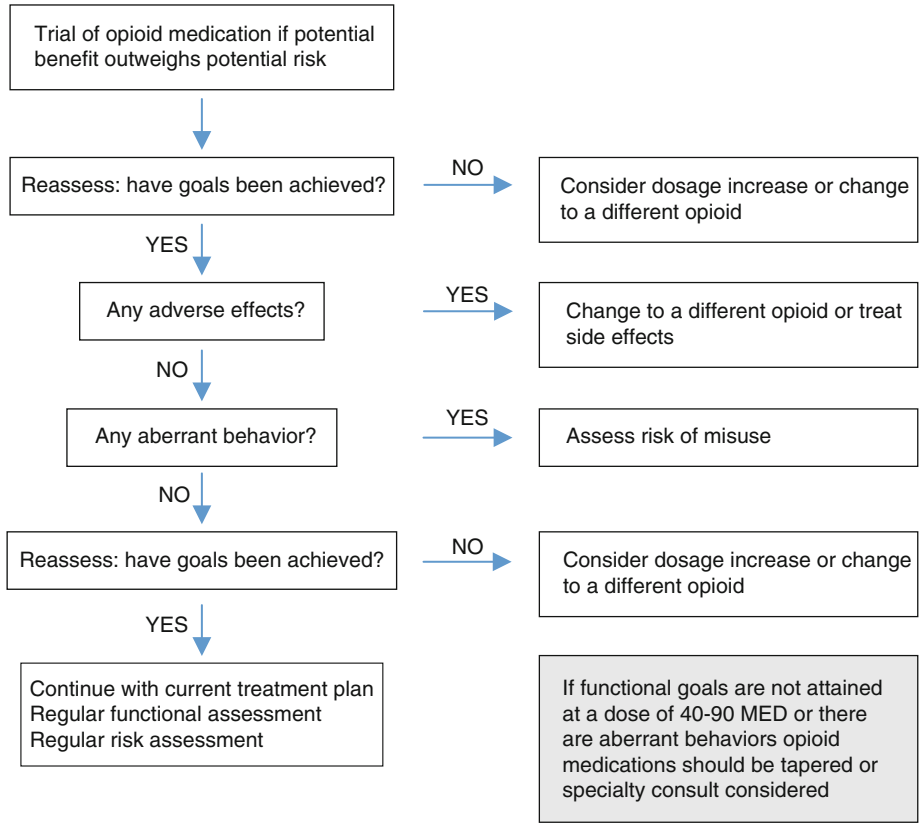

Fig. 4 MED = Morphine equivalent dose

the common adverse effects of opioids at the start of treatment. Even patients on short-term opioids should be warned about constipation and prescribed a stool softener. Chronic opioid users do not develop tolerance to constipation and may also require a stimulant laxative. Nausea is common and typically resolves with time, however antihistamines or metoclopramide will also relieve symptoms [17]. Cognitive impairment or sedation is a major risk when starting or increasing medications or when taken with other sedating substances including benzodiazepines and alcohol. Patients should be instructed not to drive at any time when they feel impaired [15]. The risk of respiratory depression and death is much higher when a patient's dose is increased or when combined with other drugs such as benzodiazepines. A discussion of the risks of physical dependence and withdrawal is also necessary.

Patients and providers should establish reasonable expectations at the start of an opioid trial. Total pain relief with opioids is not realistic. The average benefit on a 10 point pain scale is 2–3 points [15]. A successful opioid trial typically results in a 30 % reduction in pain or a 30 % improvement in function [13].

Documenting informed consent and expectations is crucial and can be accomplished using treatment agreements (pain contracts). There is some evidence that treatment agreements may improve compliance [13]. Using these agreements, providers can also discuss expectations of random urine drug testing, pill counts, replacement of lost/stolen prescriptions and counsel to avoid excessive amounts of alcohol.

Prescription monitoring programs are active in at least 48 states and can reduce doctor shopping and prescription drug abuse [13, 14]

Unfortunately these programs are grossly underutilized [13, 14].

Every patient on chronic opioid therapy should have periodic urine drug screening (UDS) [13]. The frequency of testing can be based on the patient's overall risk of misuse. Using these screens is important, however the interpretation of results is not always straightforward. Results should be considered in the context of patient behavior and overall compliance [15]. 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. Furthermore, numerous assays and platforms for UDS are available, each with variable test characteristics not equivalent across all drug classes. Not infrequently, pseudoephedrine may result in a false-positive amphetamine screen, while testing positive for cocaine is far more specific.

Discontinuation of Opioids

If patients are not progressing toward established treatment goals, show repeated aberrant behaviors, or are suffering intolerable adverse effects, discontinuation of therapy should be considered [15]. A conservative opioid taper, with weekly decreases of 10 % of the original dose, is usually well tolerated although more aggressive decreases are possible [13]. While not life threatening, opioid withdrawal can be unpleasant, and symptoms can be managed with clonidine 0.1–0.2 mg orally every 6 h or by transdermal patch at 0.1 mg weekly. Patients on clonidine should be monitored for hypotension [13]. Benzodiazepines should not be used to control symptoms during tapering [6]. Patients who are abusing the medication or noncompliant with the taper schedule should be referred for detoxification [13].

All patients with aberrant behavior should be offered addiction resources [15]. 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.

Chronic Disease Model

Chronic noncancer 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 [18]. Chronic noncancer 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 [19].

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Care of the Dying Patient

Franklin J. Berkey

Contents

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 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].

Hospice

There are more than 5,800 hospice programs in the USA today providing end-of-life care to an estimated 1.5 million patients. While cancer diagnosis previously accounted for the majority of the hospice referrals, current data reflects a broad

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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: [13]

array of terminal diagnoses. In 2013, 63.5 % of hospice admissions were for noncancer diagnosis, with dementia (15.2 %), heart disease (13.4 %), and lung disease (9.9 %) leading the list of noncancer hospice admissions [6].

Centers for Medicare and Medicaid Services (CMS) certified 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 on 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). [7] 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 avoid end-of-life conversations for fear of making patients depressed, taking away hope, and shortening life span with hospice involvement [8].

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 $\leq$ 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: [15]
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 discussions are associated with less aggressive medical care, earlier hospice referral, improved quality of life, and better bereavement adjustment [9].

The SPIKES Protocol provides a six-step plan to deliver bad news to a patient [10]. The protocol guides the provider in the four critical objectives 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 the 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 a question comes to mind*."

Prognosis at End of Life

Physicians tend to be overly optimistic when estimating survival [11]. 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" [12]. 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), a validated scale assessing overall functioning of a terminally ill patient, can assist the physician in refining the prognosis and determining hospice eligibility [14]. 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.

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 [16]. 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 [17].

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 equivalent every 4 hours. 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 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 pharmacist 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. Tramadol (Ultram), due to its action on serotonin and norepinephrine, provides relief of neuropathic pain, as well as improvement in sleep and performance status [18]. Tricyclic antidepressants (TCAs) are effective in treating neuropathic pain [19]. 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 [20]. 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 [21]. Bisphosphonates may be useful in patients with widespread bone pain, especially in patients with multiple myeloma and concomitant hypercalcemia [22]. 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 [23]. Depression is highly associated with brain, breast, lung, pancreatic, and oropharyngeal malignancies and less associated with colon and gynecologic tumors [24, 25]. 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 [26].

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 lactulose 30 ml. 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 lactulose is increased to 30 ml 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.

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 [27]. 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, and fever unresponsive to antipyretics. It is generally accepted that dying patients 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 [28].

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 or in development in all but six US states [29]. 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 [30]. 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 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 [31]. Physician-assisted suicide, legal in Oregon, Washington, Montana, Vermont, and California, 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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Family Medicine
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Headache

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General Principles

Definition and Classification

Headache is a symptom, not a diagnosis. In addition to the "primary" headaches such as migraine, tension-type or cluster, numerous conditions can cause headaches. These secondary headaches can result from systemic conditions as well as pathology in the head and neck. The International Classification of Headaches provides diagnostic criteria for multiple types of headache (Table 1) [1]. "Mixed headaches" with elements of more than one headache category are common. Individuals may also experience more than one type of headache; for example, patients with migraine often also experience tension headaches, and migraine or tension headaches can transform into medication-overuse or chronic daily headache.

Epidemiology and Impact

Two types of headache, tension and migraine, are the second and third most common diseases in the world, exceeded only by dental caries [2]. Multinational studies estimate that over 70 % of men and 86 % of women experience at least one headache per year. In men, the prevalence peaks at about 82 % in the 30–40-year age group. For women, the peak prevalence is higher (93 %) at younger ages (20–30 years) but remains high through middle age. For both sexes, headache prevalence declines with age, but 48 % of men and 62 % of women older than 60 report at least one headache per year [3]. Headache prevalence does not differ significantly by race or ethnicity but is correlated with lower educational and economic levels, lower reported general health, increased use of healthcare services, and increased number of comorbid physical and/or psychiatric conditions [3–5].

For many individuals, headaches are frequent, severe events that disrupt normal activities, impede personal advancement, and strain relationships. In the USA, 15 % of men and 28 % of women report a severe headache in the last 3 months [4]. About one third of the men and half of the women who report headache experienced symptoms at least once per week [3]. In the USA, headache was the principal cause for over 12 million office visits and was the fifth leading cause for emergency department visits in 2009 [4]. Headache patients, especially those with migraine or medication-overuse headaches, report significant negative impact on education and career success, income, personal relationships, and social activities [3–5]. Many patients perceive stigma associated with headache. Only about one third of headache patients believe that others understand and accept the condition, and at least 30 % avoid letting others know about their symptoms [3].

Approach to the Headache Patient

Despite the high prevalence and significant morbidity, the vast majority of headaches are managed without medical advice [6, 7]. Little is known about why some headache patients seek medical advice. Consultation is not correlated with the severity of symptoms [8]. Each headache episode is interpreted by

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Table 1 Headache classification [1]

Primary headaches
Migraine
Without aura
With aura (several types)
Childhood period syndromes, possible migraine precursors
Retinal
Childhood syndromes
Complications of migraine
Probable migraine
Tension type
Infrequent episodic
Frequent episodic
Chronic
Probable
Cluster and other trigeminal autonomic cephalalgias
Cluster
Paroxysmal hemicranias
Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT)
Probable trigeminal autonomic cephalalgia
Other primary headaches
Stabbing
Cough
Exertional
Sexually related
Hypnic
Thunderclap
Hemicrania continua
New daily persistent headache
Secondary headaches
Associated with
Head and neck trauma
Cranial or cervical vascular disorders
Nonvascular intracranial disorders
Substance use or withdrawal (including medication side effects)
Infection (intracranial and systemic)
Disturbance of homeostasis
Disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cranial structure psychiatric disorder
Cranial neuralgias, central and primary facial pain, and other headaches
Include various neuralgias and facial pain syndromes
Headaches due to external compression or cold
Unclassified or unspecified headaches

the individual in terms of personal experience, family influences, culture, and belief systems. A relatively minor degree of pain may prompt one headache patient to seek emergency care and comprehensive neurologic assessment, whereas another individual may cope with incapacitating symptoms over a prolonged period.

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Consultations for headache are often challenging. The patient may be dissatisfied with previous headache care, have inaccurate information, and/or have unrealistic expectations for management [7, 8]. Physicians frequently identify headache as a "heart-sink" condition, i.e., evokes "an overwhelming mixture of exasperation, defeat, and sometimes plain dislike" [9]. Physician discomfort with headache consultations may be caused or exacerbated by many factors including the subjective nature of symptoms; the recurrent, chronic pattern of most headaches; lack of confidence in treatment strategies; the potential for patients to be dependent or seeking secondary gain; possible iatrogenic complications (particularly overuse of narcotic analgesics); and fear of missing a potentially serious intracranial lesion [10]. Above all, the consultation may be handicapped by perceived or real lack of trust or respect between patient and physician. The effective management of headaches requires the development of a therapeutic alliance based on a mutually agreed plan for management and expectations for outcomes. Most chronic headache conditions are recurrent and cannot be completely cured. Physicians can, however, greatly help patients to understand their condition, develop effective strategies to reduce the number and severity of attacks, and follow healthy lifestyles not skewed by the presence or fear of headache.

With so many potential causes and complicating circumstances, a systematic approach to the headache patient is essential. This can be achieved in four stages:

1. Clarification of the reasons for the consultation
2. Diagnosis of the headache type
3. Negotiation of management
4. Follow-up

Note: A significant headache history is sometimes discovered in a patient presenting for other reasons. The approach to these patients begins with identifying why the patient has not sought medical help for headache symptoms.

Clarification of the Reasons for Consultation

Patient beliefs about headache, the burden of suffering it imposes, and concerns about the prognosis have been identified as the strongest predictors of poor outcomes of care [11]. Reasons for consultation may range from fear of cancer to seeking validation that current use of nonprescription medication is appropriate. The visit may have been precipitated by a change in the coping ability of the patient, family, or coworkers rather than any change in the severity, frequency, or pattern of headache symptoms. Patients may also consult when they learn new information, particularly about a severe illness that presented as headache in a friend, relative, or public person. Advertising campaigns may influence patients to consult physicians to request new treatments for headaches, especially for migraine. Background information from relatives and friends may give useful insights, but disruptive headaches can lead to highly charged situations, and the physician must avoid becoming triangulated between the patient and others. Patients should always be asked why they decided to seek medical advice for their headaches. With good listening and a few directed questions, the background to the consultation can be clarified and the groundwork laid for accurate diagnosis and successful management. This short time is well invested. Improved symptom outcomes as well as patient satisfaction are correlated more strongly with the physician's perceived interest and communication skills than the diagnostic or management strategies employed [8].

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Table 2 Diagnostic criteria for common primary headaches [1]

Headache	Duration	Characteristics	Associated symptoms	Others
Migraine	4–72 h each episode	At least two: Unilateral Pulsating Moderate to severe intensity Aggravated by activity	At least one: Nausea/vomiting Photophobia and phonophobia	No neurologic source for symptoms Multiple subtypes (Table 1) At least five attacks for diagnosis
Cluster	Individual attacks: 15–180 min Cluster episodes: <1–8 attacks/day for 7 days to 1 year or longer with pain-free periods	Unilateral orbital/temporal/supraorbital stabbing Severe to very severe	Restlessness/agitation At least one ipsilateral: Conjunctival injection Lacrimation Nasal congestion Rhinorrhea Facial sweating Miosis Ptosis Eyelid edema	No neurologic source for symptoms At least five attacks for diagnosis Episodic, chronic, or probable forms Related to paroxysmal hemicrania, SUNCT, and other rare syndromes
Tension type	Individual headaches: 30 min to 7 days *Infrequent* <12 days/year *Frequent* 12–180 days/year *Chronic* >15 days/month for >3 months (>180 days/year)	At least two: Pressure/tightness Bilateral Mild to moderate Not aggravated by activity	No nausea/vomiting Photophobia and phonophobia: absent or only one present, not both	No neurologic source for symptoms At least 10 episodes for diagnosis Exclude medication-overuse headache

Diagnosis of the Headache Type

Headaches are classified into four groups of "primary" headaches and multiple types of secondary headache (Table 1) [1]. Diagnosis depends on identifying the typical clinical picture for each headache type (Table 2) and eliminating other possible causes for the patient's symptoms.

The diagnosis is heavily dependent on history, particularly the patient's description of the headache symptoms and pattern. It is not uncommon for a patient to believe he/she is suffering from migraine when the true diagnosis is another type of headache. Research and treatment innovations focus heavily on migraine, but tension headaches are about three times more common in the general population [12], and secondary headaches may also be more common than migraine in patients presenting to family physicians. Intracranial pathology is a rare cause of headaches presenting to family physicians. Studies and expert groups have identified "red flags" for intracranial pathology (Table 3) mainly based on patients in emergency rooms or those consulting neurologists [13–16].

History

Headache diagnosis depends on using the medical history to identify the criteria for a specific type of headache (Table 2). An open-ended approach, such as "Tell me about your headaches," followed by specific questions to elucidate essential features usually indicates which of the diagnostic categories is most probable. Patients should be asked directly what type of headache they believe they have and what causes it. These issues must be addressed during the management even if they are inaccurate. Patients should also be asked about previous investigations and treatments and their current expectations of management. The history should cover the following areas:

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Table 3 Conditions associated with increased odds of significant abnormality on neuroimaging [13–16]

Cluster headache
Abnormal neurological examination
Undefined headache (not meeting criteria for migraine, cluster, or other primary headaches)
Headache with aura or vomiting
Headache exacerbated by exertion or Valsalva maneuver
Sudden onset of new headache especially in patients older than 50 years
Rapidly increasing headache frequency
Headache that wakens from sleep
Patients with cancer, HIV, systemic illness, or other condition increasing vulnerability to intracranial pathology

1. *Characteristics*: nature of pain, location, radiation in head, intensity, exacerbating and relieving factors or techniques, associated symptoms and signs
2. *Pattern*: usual duration and frequency of episodes, precipitating factors, description of a typical episode, change in pattern over time, prodromes and precipitating factors, post-headache symptoms
3. *Personal history*: age at onset; medical history (including medication, alcohol, and substance use) with special emphasis on secondary causes of headache, such as depression or trauma; environmental and occupational exposure history
4. *Investigations and treatments*: previous headache diagnoses and supporting evidence, patient's degree of confidence in these diagnoses, patient's beliefs and concerns about diagnosis and potential treatments, previous treatments and degree of success, side effects of any investigations and treatments, patient preferences for treatment, and current use of prescription and nonprescription medications
5. *Family history*: headache, other conditions, family attitudes to headache
6. *Review of systems*: special focus on "red flag" symptoms and symptoms indicating a neurological, systemic, or head and neck condition that could cause a secondary headache

The headache profile that emerges from the history has a high probability of correctly classifying the headache. It is important to complete the review of systems to uncover additional information, particularly any neurological symptoms and comorbid conditions. Patients should be directly asked for any symptoms of "red flags" indicating potentially serious secondary headaches. Throughout the history, the physician forms a general impression of the patient. Although subjective, this helps in assessing the patient's understanding of the headache and receptiveness to management strategies.

Physical Examination

The physical examination continues the process of confirming a specific diagnosis, ruling out alternative explanations for symptoms, and laying the groundwork for successful management. Unless the consultation coincides with an attack, most migraine, cluster, and other headache patients have no abnormal findings on physical examination. Expert recommendations stress the importance of a thorough, documented neurological examination at baseline that is repeated if necessary as clinical signs may evolve over time [13–15]. If the history suggests a source of secondary headaches, an appropriate targeted examination should be done, e.g., of the head and neck in the case of an adult with sinus symptoms or an older patient with temporal arteritis or cervical osteoarthritis. The time devoted to physical examination is a wise investment, as it documents both positive and negative physical findings, contributes to the therapeutic alliance, and is often itself reassuring and beneficial to the patient.

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Diagnostic Investigations

Current expert guidelines report "insufficient evidence" to support any specific laboratory or neurophysiological testing, including EEG, in headache evaluation (with a few exceptions for rare conditions) [13]. In individual patients, specific laboratory tests may be indicated to confirm a secondary headache diagnosis suggested by the history and physical examination. Nevertheless, tests are often performed to relieve either physician or patient distress and uncertainty. If the patient or family insists on testing, the concerns and motivations of the patient/family should be explored and the potential contributions and limitations of the requested test(s) reviewed. Similarly, the physician experiencing the WHIMS (what *have I* missed syndrome) should review the data and attempt to make a rational decision as to the potential contribution, cost, and risks of additional testing.

Neuroimaging

Most of the debate over the appropriate role of testing involves radiologic investigation, especially computed tomography (CT) and magnetic resonance imaging (MRI). The role of neuroimaging is limited by the rarity of intracranial lesions in patients presenting to family physicians and hence the very low yield of imaging in unselected headache patients. Serious intracranial pathology has been estimated to cause less than 1 % of new headaches presented to primary care physicians [17] and 1–2 % in patients presenting to neurologists [18–20]. A British study estimated the risk of brain tumor in headache patients presenting to family physicians as 0.09 % [10]. Any potential benefit from neuroimaging must be considered in light of radiation exposure (for CT), patient distress, cost, and the implications of false-positive or noncontributory incidental findings. As various imaging modalities have different characteristics, the physician should have a clear concept of the type and location of any suspected intracranial condition in order to select the most appropriate investigation. Non-contrast CT is very sensitive to acute hemorrhage and certain enhancing solid lesions; MRI provides better resolution in the posterior fossa and superior detection of gliosis, infection, posttraumatic changes, and certain tumors [16]. Other imaging modalities may be indicated for specific circumstances [14–17]. Discussions with a radiologist may be useful before ordering tests.

Current guidelines state that neuroimaging is only indicated if "red flag" conditions are present (Table 3) [13–17]. Although neuroimaging should only be used if the patient has a significant risk of a relevant abnormality and the result is likely to change clinical management, it is often considered in patients who are excessively anxious about the cause of their headaches. The few studies on patient anxiety and satisfaction with headache care indicate that the interaction with the physician is by far the most important factor in improving outcomes. Imaging does not significantly reduce anxiety or improve satisfaction with care [8, 10]. One intriguing study of patients with chronic daily headache and high levels of anxiety and depression concluded that the primary benefit of imaging was in reassuring primary care physicians: the patients did not obtain long-term psychological or physical benefit from imaging [21].

Negotiation of Management

As migraine, cluster, tension/stress, and many secondary headaches are chronic conditions, appropriate management goals are:

- Providing effective treatment of individual headache episodes
- Minimizing the number and severity of headache episodes
- Optimizing patient function and self-care
- Minimizing adverse effects of treatment
- Optimizing cost-effective use of resources [13]

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Most headache patients are open to the concept that they carry a vulnerability to headaches and are willing to learn how to manage this tendency. Patients who strongly resist this approach may have dependent personalities, secondary gain from their headaches, and/or have drug-seeking behavior. The complete management plan includes patient education, treatment plans for both prophylaxis and acute management, and follow-up.

Patient education is essential for the patient and family to manage headaches. They must understand the type of headache, treatment options, and likely prognosis. In addition to providing information, the physician must address hidden concerns. Many myths and beliefs are associated with headache and its treatment. Patients can better manage their headaches once these beliefs are addressed [8]. Patients may be embarrassed by their fears; for example, almost all migraine patients have feared cerebral hemorrhage during a severe attack. Patients gather information about headaches and their treatment from a wide variety of sources, including the Internet, news media, and the experience of friends. Reliable websites may be recommended (see Patient Resources), and the patient warned that the Internet accesses a great deal of misleading and potentially alarming or harmful information about headaches.

One aspect of patient education is identifying and managing situations that precipitate or exacerbate headaches. These situations range from avoiding foods that trigger migraine episodes to practicing conflict resolution. Stress is implicated in almost all headaches; even the pain of secondary headaches is less easy to manage in stressful situations. Formal therapies such as relaxation therapy, thermal biofeedback, and cognitive-behavioral therapy can be effective in individual patients. Practical advice can be helpful in building the placebo effect and therapeutic alliance. Physicians gather experiences from many patients and can pass on tips such as Lamaze-type breathing exercises for tension headaches, cold washcloth over the eyes during a migraine attack, and even attempting vigorous exercise to abort migraine, cluster, or tension headaches. Including such information in the overall treatment plan enhances the physician's credibility and reinforces the message that headache management is not solely dependent on medications.

There are few "absolutes" in the pharmacologic treatment of headaches, and the large number of choices can be bewildering to both physicians and patients. Treatment is specific to the type of headache diagnosed (see below). In general, first-line analgesics and symptomatic treatment are effective, and narcotic use should be avoided. A common mistake is to appear tentative about therapy. The exasperated physician who uses phrases such as "We'll try this" may convey the message that the medication is not expected to work. Conversely, conveying that one has used the scientific literature and expert guidelines to select a medication specific to the individual patient is much more likely to succeed.

Follow-Up

With the exception of headaches secondary to acute self-limiting conditions, headache tends to be a recurrent problem. Unless follow-up is well managed, the patient may return only at times of severe symptoms and/or exasperation at treatment failure. This risks emergency visits complicated by hostility and mutual disappointment. Many patients can manage well if given scheduled appointments, particularly if they are combined with the expectation that the patient will come to the consultation well prepared (i.e., with information on the number, pattern, response to treatment, and any other relevant information about headaches since the last visit). Some authors recommend a formal headache diary to help track changes in the headache pattern over time and monitor for adverse effects of treatment. Headache management requires continuous adjustments, a high index of suspicion for the many conditions that have increased prevalence in headache patients, and promoting a healthy lifestyle. Optimizing general health has a positive impact on headache frequency, severity, and ability to cope with symptoms.

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Clinical Types of Headache

Migraine

Migraine-type headaches (Table 2) are estimated to affect approximately 17 % of women and 8 % of men in the USA [6, 22]. The median age at onset is about 24 years [23] and migraine is most prevalent in young adults [6, 22, 23]. Longitudinal studies indicate very high vulnerability to migraine in the general population with over 40 % of women and 18 % of men reporting at least one migraine during their lifetimes. Researchers suggest that the migraine tendency may be very prevalent and that "induction factors" in early adult life determine which individuals develop clinical migraine. Epidemiological studies implicate various possible genetic, hormonal, or social factors in this process [23]. The vast majority of migraine patients have a first-degree relative, often a parent, who also has migraine. Perhaps because of this familiarity with the condition, at least a third of migraine sufferers have never sought medical assistance for the condition [6].

The headache of migraine is severe, usually unilateral, "throbbing," or "pulsating," and aggravated by movement. The pain usually takes 30 min to 3 h to reach maximum intensity, and it may for last several hours. The eye and temple are the most frequent centers of pain, but occipital involvement is common. The typical headache must be accompanied by nausea and/or vomiting plus both photophobia and phonophobia for diagnosis (Table 2). Additional symptoms such as fatigue, vertigo, and allodynia are common. Many migraine patients describe a prodrome in the days before a migraine when they feel irritable, restless, intensely hungry, or excessively fatigued in the "run-up" to an attack. About 20 % of patients experience consistent, specific neurological changes (aura) up to an hour before the onset of migraine headache. The most common forms of aura are visual scotoma, flashing lights, and/or zigzag lines, but a wide variety of other features have been reported such as paresthesia, speech disturbance, and disorders of body perception. The severity, duration, and impact of migraine attacks vary enormously. Some patients are able to continue normal activities whereas others are incapacitated. During attacks, migraine patients avoid movement and sensory stimuli, especially light. Most go to bed in a dark room if possible. They may use pressure and either heat or cold over the areas of maximal pain. The attack usually terminates with sleep. Vomiting appears to shorten attacks, and some patients admit to self-induced vomiting, although this is not widely described in the literature. Many patients report a "hangover" after a migraine, but others experience freedom from symptoms and a sense of mild euphoria.

Diagnosis is based on history. The diagnostic probability is 92 % if four "POUND" symptoms are present – Pulsating or throbbing headache (1 day duration (4–72 h)), Unilateral location, Nausea or vomiting, and Disabling severity. This probability falls to 64 % for three symptoms and 17 % for two or less [24]. Imaging is not indicated in migraine patients who have normal neurological examination and no red flag findings [14–17]. Research shows that imaging identifies significant findings in about 1 % of migraine patients referred to specialist centers and lower levels in patients presenting to primary care [17, 26].

The cause of migraine remains unknown, but research indicates that the process begins as a wave of neuronal depolarization that triggers complex neurochemical, vascular, and other changes resulting in activation of the trigeminovascular system. The symptoms experienced depend on which parts of the system are activated as well as its interconnections with other parts of the brain and nervous system.

The treatment of migraine is based on enabling patients to manage their own condition. A bewildering variety of therapies is available, and management should be individualized. The treatment plan has three aspects: avoidance of precipitants, optimal treatment of attacks, and prophylactic therapy if indicated. Patients and their families can usually identify triggers of migraine attacks. The role of specific foods has probably been exaggerated, although red wine and certain cheeses continue to have significant reputations as migraine triggers. Disturbance in daily routine, particularly missed meals, excessive sleeping, and

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relaxation after periods of stress, are common precipitants of migraine attacks. Some women correlate migraine with the onset of menstruation each month, but the effect of oral contraception and postmenopausal hormone replacement is unpredictable. Migraines commonly disappear during pregnancy.

Patients should be encouraged to recognize their own aura or prodrome, as early treatment is most effective. The multiple medications used for migraine may be categorized into three groups:

1. Symptom control: analgesics, with or without adjunctive antiemetics or sedatives
2. Triptans: serotonin (5-hydroxytryptamine, 5-HT) receptor agonists
3. Ergotamines and other medications

A common problem in migraine treatment is subtherapeutic dosage of medication or failure to absorb medication because of vomiting and gastric stasis. European guidelines include metoclopramide or domperidone (level B recommendation) for antiemetic and mild analgesic effects as well as possibly improving absorption of other medications [25].

The USA and newer European guidelines found strong evidence to support the use of several different medications in acute migraine (Table 4). The choice of medication(s) and route of delivery must be individualized based on the migraine pattern (particularly the likelihood of vomiting), patient factors such as other medical problems, and medication issues including efficacy, speed of onset, side effects, cost, and acceptability. Guidelines stress the balance between effective treatment and avoiding iatrogenic effects from inappropriate medication use [13, 25]. Patients frequently appreciate having more than one agent or combination of agents available, e.g., an analgesic or a triptan to use when they need to "keep going" and a combination of analgesic and sedative for situations when they can "crash." Many patients also report that a specific medication works well for several months but then becomes less effective.

Narcotics have almost no place in migraine therapy. Even in the emergency room situation, adequate analgesia, triptans, injections of antiemetics, or injectable ergotamines are superior to narcotics [26]. The migraine patient who demands narcotics or claims allergies to alternative treatments may be drug seeking. Rarely, patients develop dehydration and "status migrainosus" when the attack lasts several days. These patients may require steroids in addition to fluids and aggressive therapy based on antiemetics plus a triptan or ergotamine.

For most patients, analgesics with or without antiemetics are the first choices for treatment. Some experts advocate triptans as first-line treatment for more severe cases [27]. In studies, triptans are comparable or only marginally more effective than adequate analgesia. They benefit about 60 % of patients who do not respond to NSAIDs [25]. The various triptans appear to be equally effective but vary in speed of onset and duration of action. This allows selection of a specific triptan that matches the patient's typical migraine attack, especially in selecting one with a long half-life for patients who experience slowly developing symptoms that persist over several days or who experience significant rebound headaches. Treatment should be started early in a migraine attack, but triptans are not effective and are reported to be potentially dangerous if taken during aura [25]. Depending on the medication used, up to 40 % of patients experience recurrence of symptoms after initial improvement. This "rebound headache" often responds to a second dose of the initial treatment. Combining an NSAID with a triptan as initial therapy reduces recurrence [25].

If patients find normal life disrupted by the frequency and severity of migraine attacks, prophylactic treatment should be considered. An estimated 38 % of migraine patients could benefit from prophylactic treatment but less than 13 % currently use it [28]. Good efficacy has been demonstrated for several beta-blockers and antiepileptic drugs. Other agents, especially some antidepressants, are probably effective (Table 4). A recent US guideline also found good evidence supporting the herbal therapy petasites (butterbur) with more limited evidence for some NSAIDs, magnesium, feverfew, and riboflavin

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[29]. The dosage at which individual patients benefit must be established by weeks or months of monitoring of frequency and severity of migraine attacks plus any adverse effects. Some behavioral therapies such as thermal biofeedback, relaxation training, and cognitive-behavioral therapy are recommended as preventive interventions and may be combined with prophylactic medications [13, 30]. Patient compliance is crucial to prophylactic therapy. The choice of any prophylactic agent must

Table 4 Pharmacologic treatment of primary headaches [13, 25, 28, 29]

Headache type	Acute attack		Prophylactic therapy	
	Agent and dose	Comment	Agent and dose (per day)	Comment
Migraine	Analgesics[a] Aspirin 650–1000 mg Acetaminophen <1000 mg Ibuprofen <800 mg Naproxen 500–1000 mg Ketorolac 30–60 mg IM	Dosage individualized Combinations available with sedatives and antiemetics	Beta-blockers Propranolol 40–240 mg Timolol 20–30 mg Metoprolol 50–200 mg Atenolol[b] 50–100 mg Nadolol[b] 80–240 mg	Dosage individualized; side effects fatigue, Gl upset; contraindicated with asthma, heart failure
	5-HT agonists[c] Sumatriptan 6 mg SC 25–100 mg oral, 5–20 mg nasal Zolmitriptan 2.5–5 mg oral or nasal Naratriptan 2.5 mg Rizatriptan 5–10 mg Almotriptan 12.5 mg	Moderate to severe Contraindicated in cardiovascular, cerebrovascular risk, pregnancy Not given during aura May be combined with NSAID	Antiepileptics Valproic acid 600–1800 Topiramate 25–100 mg	Teratogenic, hepatic, skin, GI effects Weight loss
			Antidepressants Amitriptyline 50–150 mg[b] Venlafaxine 75–150 mg[b]	Sedation, weight gain, dry mouth; synergistic with beta-blockers
	Ergotamines Inhalation (0.36 mg/dose) Oral, sublingual (1–2 mg)[b] DHE SC/IM/IV (0.5–1 mg)[b]	Side effects: nausea, vasoconstriction Useful for status/ER	Complementary agents Petasites (butterbur) Magnesium[b] Feverfew[b] Riboflavin[b]	Doses difficult to establish
			NSAIDs Ibuprofen[b] Ketoprofen[b] Naproxen[b]	
Cluster				
	Oxygen 100 % 7–15 mL/min Sumatriptan 6 mg SC Sumatriptan 20 mg nasal Zolmitriptan 5 mg nasal Lidocaine 4 % 1 ml nasal[b]		Verapamil 240–960 mg daily Prednisone <100 mg for 5 days then taper Lithium 600–1500 mg daily[b] Topiramate 25–100 mg/day[b]	

(*continued*)

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Table 4 (continued)

Headache type	Acute attack		Prophylactic therapy	
	Agent and dose	Comment	Agent and dose (per day)	Comment
Tension				
	Ibuprofen 200–800 mg Ketoprofen 25 mg Aspirin 500–1000 mg Naproxen 375–550 mg Acetaminophen 1000 mg		Amitriptyline 30–75 mg Mirtazapine 30 mg[b] Venlafaxine 150 mg[b]	

Level A recommendations unless otherwise noted

[a]Simple analgesic restricted to 15 days/month: combination analgesics restricted to 10 days/month to prevent medication-overuse headache

[b]Level B recommendation (probably effective)

[c]Triptans restricted to 9 days per month. Significant danger of medication-overuse headache after 12 days/month

Treatment must be of rapid onset. (1) All therapy should be started at first sign of attack, but triptans are not advised during aura. (2) Other symptomatic relief may be added, especially antiemetics and sedative. (3) Encourage patients to find abortive therapy (e.g., caffeine, exercise, cold ± pressure over the site or pain) to use in addition to above. (4) Narcotics are rarely necessary for migraine

5-HT 5-hydroxytryptamine (serotonin), *NSAID* nonsteroidal anti-inflammatory drug

AAFP treatment guidelines are available at http://www.aafp.org/afp/20001115/practice.html

balance potential benefit against issues of compliance, side effects, and cost. Migraine patients can usually be assisted to find regimens that enable them to minimize attacks and deal effectively with those that do occur. They may be comforted by knowing that the condition tends to wane with age and has afflicted a galaxy of famous people.

Cluster Headaches and Other Trigeminal Autonomic Cephalalgias

The updated international classification [1] recognizes that cluster headache is part of an uncommon group of conditions in which activation of the trigeminovascular system is associated with reflex autonomic activation. The three clinical syndromes of cluster headache, paroxysmal hemicranias, and short-lasting unilateral neuralgiform attacks with conjunctival injection and tearing (SUNCT) are characterized by brief, unilateral, severe headache plus cranial autonomic symptoms such as conjunctival injection, lacrimation, nasal congestion or rhinorrhea, facial sweating, miosis, or ptosis [1, 31]. Cluster headache has an estimated prevalence of less than 1 % of adults and is more common in men. The average age at onset is 28–30 years, but it can start at any age and is persistent with 80 % of patients still experiencing attacks 15 years after the initial episode [32].

The headache is severe, unilateral, centered around the eye or temple, and accompanied by lacrimation, rhinorrhea, red eye, and other autonomic signs on the same side as the headache. Symptoms develop rapidly, reach peak intensity within 10–15 min, and last up to 2 h. During the attack, the patient is restless and may be suspected of intoxication, drug-induced behavior, or hysteria. The diagnosis is based on the description of attacks, especially their severity, and is confirmed by the unique time pattern. During a cluster period, which typically lasts 6–12 weeks, the patient experiences attacks at the same time or times of day or night with bizarre regularity. Most patients report one or two cluster periods per year (often in spring and autumn) and are completely free from symptoms at other times. About 10 % of patients develop chronic symptoms, with daily attacks over several years. During a cluster period, drinking alcohol or taking vasodilators almost inevitably precipitates an attack. Cluster headache may be due to a disorder of serotonin metabolism or circadian rhythm (or both), but the cause remains unknown [32, 33].

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Management strategies aim to provide relief from individual attacks and prophylactically to suppress cluster episodes (Table 4). Acute treatment must be of rapid onset and able to be administered by the patient or family. Conventional analgesics do not act quickly enough to provide relief, and all treatments can be difficult to administer to a patient who is restless and distracted with pain. Inhalation of oxygen at least 7 l/min with a non-rebreathing facial mask is effective in about 60 % of cases (level A recommendation). Hyperbaric oxygen appears ineffective [31]. If the patient has no contraindications, subcutaneous sumatriptan (6 mg or less) is reported to be about 75 % effective [31]. Although less evidence is available, triptan nasal sprays (sumatriptan, zolmitriptan) appear to be effective. Recent studies found subcutaneous octreotide (100 ug) effectively terminated cluster attacks [31]. Older treatments including nasal lidocaine and oral or intranasal ergotamine are useful but have not been extensively researched [31].

The mainstay of cluster headache management is to suppress attacks during a cluster period. The first-line agent is verapamil, but patients must be monitored for possible adverse cardiac effects. Steroids may also be effective for short periods. Clinical studies have reported mixed effectiveness for lithium with older studies reporting it to be as effective as verapamil, but newer studies are not confirming this outcome. Other drugs with limited evidence of effectiveness in suppressing cluster include methysergide, topiramate, valproic acid, and melatonin [31]. Prophylactic treatment should be initiated as soon as a cluster period begins and continued for a few days beyond the expected duration of the cluster. Only the previous experience of each patient can be used to judge the duration of therapy. Each patient has a set length for the cluster period as well as a tendency to repeat the same time and symptom pattern of individual headaches. It is particularly important in the age group usually affected by cluster headaches to monitor for potential cardiovascular adverse effects associated with several of the recommended medications for acute and prophylactic use.

Tension-Type Headaches

Tension-type headaches (TTH) are the most common of all headaches and impose the greatest burden on individuals and society. Compared to migraine, direct costs for TTH are 54 % higher and three times as many work days are lost [12]. Most patients have infrequent episodes of TTH that are managed without medical assistance; however, about 10 % of individuals with TTH report headaches at least weekly. The average age of onset of TTH is 25–30 year with the peak prevalence in the 30–39 age group. Women are slightly more impacted than men (sex ration 5:4). Poor general health, problems relaxing, and difficulty sleeping are related to TTH [34].

The classification into acute or chronic is based on frequency of episodes (Tables 1 and 2), but this is more significant than the timing and pattern of the condition. It correlates with the impact on patients and indications for prophylactic therapy. The pathophysiology may also differ. Chronic TTH may result more from chronic central pain mechanisms than the peripheral processes underlying episodic and milder TTH [35].

Although TTH is the most common form of headache seen in family practice, these patients represent a select group of all TTH sufferers. The vast majority of individuals self-manage their TTH symptoms. The pain is classically described as bilateral, pressure, or tightening of mild to moderate intensity. Sometimes described as "featureless," TTH is characterized by the lack of accompanying symptoms that could indicate a migraine, cluster, or secondary headache, especially one due to a neurological disorder [35]. The diagnosis requires a good history, supplemented if necessary by a headache diary, and a negative physical examination with any necessary additional investigations to exclude secondary headache. Careful documentation of analgesic, triptan, or ergotamine intake is essential to rule out medication-overuse headache. As with all headaches, the history must screen for "red flags" and comorbidities. Over 90 % of patient with migraine also have TTH and TTH is a predictor for depression and anxiety [12].

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The treatment of tension headaches can be challenging. Success depends on treating any underlying or associated condition (particularly depression), patient education about TTH, and control of symptoms without creating dependence or other adverse effects. Patients may have already been investigated extensively, and prior medical experiences color expectations and evaluation of management approaches.

Individual episodes of TTH are best managed by first-line analgesics, such as acetaminophen, aspirin, ibuprofen, or another NSAID. Some studies indicate that NSAIDs may be more effective than other analgesics, but no difference in efficacy has been demonstrated among different NSAIDs [35]. The principal potential adverse effects are gastrointestinal bleeding for NSAIDs and liver injury for acetaminophen. To avoid medication-overuse headache, analgesics should not be used on more than 14 days per month [35]. Narcotics and combination drugs, especially those that contain barbiturates or caffeine, should be avoided. Triptans and muscle relaxants do not have good evidence of efficacy in uncomplicated TTH [35].

Prophylactic therapy is appropriate for patients with chronic TTH or those who have disruptive episodic TTH, believe they could benefit, and are willing to adhere to daily therapy. Based on a few studies, the best evidence supports amitriptyline to reduce headache frequency and intensity. A systematic review concluded that mirtazapine was as effective as amitriptyline for chronic TTH [36]. This review found other antidepressants and anticonvulsants to have "unknown effectiveness" and rated botulinum toxin and benzodiazepines as "likely to be ineffective or harmful" [36]. Similarly, cognitive-behavioral therapy and acupuncture were of "unknown effectiveness," and both chiropractic and osteopathic spinal manipulations were "likely to be ineffective or harmful." This review and another review [37] found little evidence to support biofeedback but a larger meta-analysis, and the European guidelines found a positive effect from biofeedback, especially in younger patients and if combined with relaxation training [35, 38]. The European guidelines recommend biofeedback and/or relaxation training for tense patients with TTH and cognitive-behavioral therapy for those with psycho-behavioral issues or affective distress [35].

Outcomes in TTH are often disappointing. Drug efficacy in acute attacks is modest in studies (about 30 % pain-free at two hours) [35]. Long-term studies report that a third of patients with chronic TTH were unchanged after 10 years, with an additional 20 % developing medication-overuse headache. In the same time period, a quarter of patients with episodic TTH converted to chronic forms [39].

Secondary Headaches

Headache is part of the clinical picture of many conditions. Particularly in children, frontal headache is a common accompaniment of fever. In all age groups, almost any condition of the head and neck and several systemic conditions can present as headache. A careful history combined with physical examination and other investigations where appropriate is essential to differentiate secondary from primary headache.

Family physicians face the challenge of not missing the rare but serious intracranial condition, especially brain tumor. The symptoms of an intracranial lesion depend on its type, size, location, and displacement effect on other tissues. No single characteristic headache picture can therefore be given. Suspicion should be raised about headaches of recent onset that appear to become steadily more severe, do not fit any of the primary classifications, and do not respond to first-line treatment. Close follow-up and repeated physical examinations may detect the earliest neurologic abnormalities. A review identified potential predictive features for intracranial abnormality as undefined-type or cluster headaches, the presence of aura or vomiting, headaches exacerbated by exertion or Valsalva maneuver, and any abnormal findings on neurological examination [15]. This concurs with US guidelines that also report increase odds of finding abnormality in patients with rapidly increasing frequency of headache, discoordination, or headache causing wakening from sleep [13]. Even in selected patients, these are weak predictors and the yield from imaging is low [10].

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Medication-Overuse Headache

A growing concern for family physicians is medication-overuse headache (MOH), defined as chronic headache (at least 15 days per month) in patients who have taken excessive headache-related medication for at least 3 months during which time headache symptoms have increased. The headache resolves or returns to the original pattern within 2 months of discontinuing the overused medication [1]. Medication-overuse headache can originate in tension, migraine, or any secondary headache and can result from use of analgesics, triptans, or ergotamines [40]. By some estimates, up to half of patients with chronic headaches suffer from MOH, and MOH is the leading diagnosis of patients attending specialized headache clinics [40, 41]. Medication-overuse headache is more common in women (male/female ratio 1:3.5) and appears to be related to several psychiatric disorders, low coping skills, and dependency-related behavior [41]. Perhaps because of this combination of chronic symptoms and impaired ability to cope, MOH imposes the greatest burden on patients and families of all headaches. Personal annual costs are triple those for migraine and ten times greater than for TTH. Most of this cost was indirect in terms of lost productivity and inability to carry out usual activities [2]. Patients with MOH significantly outscored those with migraine or TTH on all measures of negative life impact and were ten times more likely than migraine patients to report breakdown of relationships due to headache [2].

While the exact mechanism of MOH is unclear, it probably involves central sensitization and dysfunction in pain networks. Biochemical, pharmacological, and imaging studies all provide evidence of reversible central pain system changes induced by medications in vulnerable patients [41].

The patient often has difficulty describing precise characteristics of MOH beyond that it is severe, intractable, and debilitating. The headache and related symptoms may change from day to day. Apart from chronicity and burden, the key features in the history are experience of an established prior headache pattern (usually migraine or TTH or both) and escalating high intake of headache-related medication. It is important to document the quantity and different types of medications used, including nonprescription medications and substances obtained illegally, to get a complete picture of the extent of medication use. Screening for depression, anxiety, or another psychiatric condition may be indicated.

No expert guidelines have been developed for the investigation of MOH. Because the symptoms may be severe, changing, and not related to criteria for one of the primary headaches, physical and neurological examinations are necessary to detect any indicators of secondary headaches, especially intracranial conditions. Many patients report conditions that meet the guidelines for imaging, but decisions to obtain imaging must be individualized. The rate of detection of abnormalities in all "indeterminate" headaches investigated by specialist centers is about 3 %, but no data are available on patients with probable MOH [19].

The treatment of MOH requires withdrawal ("detoxification") and institution of effective treatment for the underlying headache. No clear advantage has been demonstrated with abrupt versus tapered withdrawal for most medications, but guidelines recommend tapered withdrawal for opiates, barbiturates, and benzodiazepines [40]. Withdrawal symptoms such as headache, nausea, restlessness, tachycardia, and anxiety can resolve in 2 days or last several weeks. Withdrawal appears shorter from triptans (average 4 days) than NSAIDs (average 9.5 days). Most patients can be managed in primary care with symptomatic treatment. Some protocols include oral steroids during withdrawal. No significant improvement in outcomes was demonstrated in comparisons of inpatient withdrawal, but it is recommended for patient with significant symptoms and/or comorbidities as well as those withdrawing from opiates, barbiturates, or benzodiazepines [40]. Effective prophylaxis for the underlying headache should be started as soon as possible in MOH. Limited data support topiramate or valproic acid in MOH developing from migraine [40].

Despite good initial results of treatment with about 75 % of patients successfully detoxifying, the relapse rate is about 30 % within 1 year and may be 60 % at 4 years [40, 42]. This does not appear to be

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related to treatment but might be related to male sex, use of analgesics (especially combinations containing codeine), poor quality of life, use of alcohol and/or tobacco, and years of experiencing headache [40].

Specific Headache Syndromes

The international headache classification system describes criteria for several uncommon primary headache syndromes that are often named for their character ("thunderclap," "stabbing") or precipitating event ("cough," "exertional") (Table 1). These syndromes are more common in men and are characterized by the severity of the pain and the potential for confusion with serious intracranial conditions [1]. Despite the sometimes dramatic history, the conditions are generally benign with the exception of thunderclap headache. Physical examination, testing, and neuroimaging may be necessary to confirm the specific diagnosis. Some of these syndromes are very responsive to indomethacin. For others explanation, reassurance, avoidance of precipitants, and symptom control are usually effective.

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Resources for Patients

American Headache Society Committee for Healthcare Education (ACHE).. http://www.achenet.org

National Headache Foundation. http://www.headaches.org

National Institute of Neurological Disorders and Stroke. http://www.ninds.nih.gov/disorders/headache/headache.htm

Several other websites are available but tend to provide recommendations especially about complementary and alternative treatments that are not evidence-based.

Seizure Disorders

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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 0–17 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 antiseizure 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 generailzed 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 % and 80 % in adults (Fig. 1).

Generalized Seizures

Generalized seizures are conceptualized rapidly engaging bilaterally distributed networks involving both hemispheres. Such bilateral networks can include cortical and subcortical structures. On

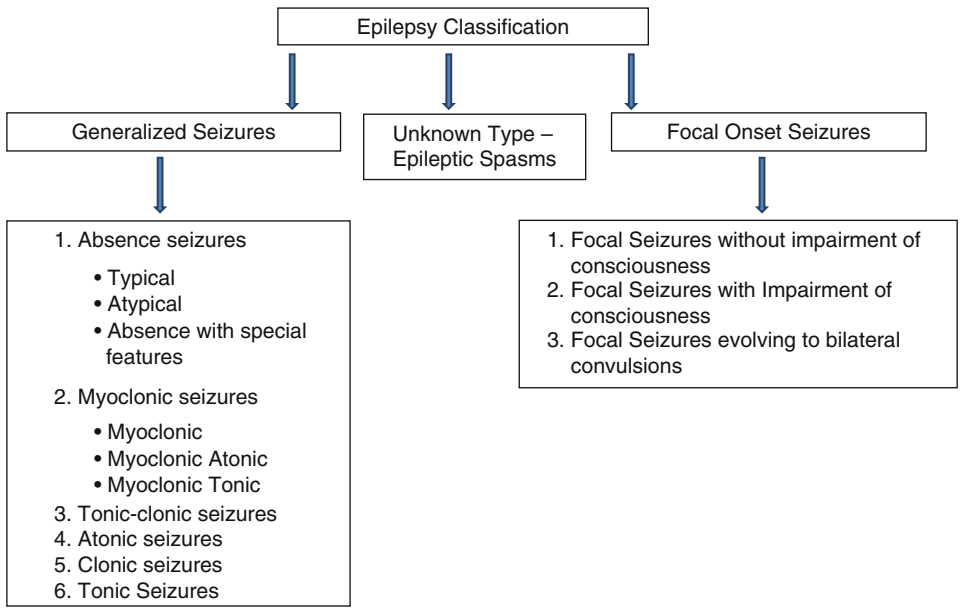

Fig. 1 Classification of Seizures

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 stiffening of all four extremities in the tonic phase and rhythmic shaking of 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. 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 postictal period the length of which is variable. The first step of diagnosing epilepsy is obtaining a detailed description of the aura (warning before a seizure), ictus (the actual seizure), and postictal 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 different features which placed them in different categories.

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.

Majority of the seizures last between 5 and 20 s. Seizure onset is sudden, and the child becomes motionless with a vacant stare. The eyes may drift upward, 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 per day.

Hyperventilation (for about 2 mins) tends to provoke these seizures and can be used in a clinic setting as a diagnostic tool as well, but caution is advised.

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 and 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 referred to as an "ictal cry." This is referred to as a tonic phase of 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 into 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 nonepileptic. Myoclonus can occur physiologically when patients are falling to sleep. Myoclonic seizures are characterized by brief, sudden, involuntary muscle contractures involving different combinations of head, trunk, and limbs. On EEG the generalized spike wave or polyspike and wave discharges are noted with these myoclonic jerks.

The commonest type of myoclonis epilepsy is juvenile myoclonic epilepsy (JME). This type of epilepsy starts in the teenage years; it is obviously characterized by myoclonic seizures, 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 postictal 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 terms *simple* and *complex* was misleading to the patients 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.

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 of an aura which is specific and stereotypical. The patient will have a sudden behavioral arrest along with automatism as well in certain cases. Automatisms consist of 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 which is specific in severe typical with spread of the seizure activity 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.

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
	Postictal – confusion and 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
Parietal lobe seizures	Paraesthesias
Occipital lobe seizures	Visual phenomenon

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
- Myclonic encephalopathy in non-progressive disorders
- Benign familial infantile epilepsy

Childhood
- Febrile seizures plus
- Panayiotopoulos syndrome
- Benign epilepsy with centro-temporal spikes (BECTS)
- 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 3rd 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 and three 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 reveals a characteristic pattern of "burst suppression."

Early Myoclonic Encephalopathy

These occur typically within the first 1 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 tends 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 to 3 years of age, and patients eventually outgrow this. There is sudden jerking of the extremities along with eyedrops which make it look like infantile spasms. The EEG however shows a generalized spike and polyspike pattern instead of the classical hypsarrhythmia seen in infantile spasms. Also they have a normal development which clearly distinguishes this from infantile spasms. The treatment is Valproate, levetriacetam, or clonazepam.

Seizures in Childhood

Febrile Seizures

These occur between 6 months to 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

Eighty to ninety percent 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.

Complex Febrile Seizures

The seizure duration is greater than 15 min. There are focal seizure manifestations or seizure recurrance within 24 h. Abnormal neurological status of the child and a family history of epilepsy. These seizures 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 %). About half of those one third will have a third febrile seizure (7–30 %). Higher recurrence 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 (SMEI)

Dravet syndrome appears during the first year of life with frequent febrile seizures and is rare

beyond age 5. Later, other seizure types arise, including myoclonus. Status epilepticus may also occur. Children with Dravet syndrome typically experience poor development of language and motor skills and hyperactivity. There is a genetic cause identified – SCN1A mutation or copy number variant in 80 % of cases. Usually pharmacoresistant. Sodium channel medications can make seizures worse. Treatment with valproate, Topamax, and Stiripentol.

Rolandic Epilepsy or Benign Epilepsy With Centrotemporal 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 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 centrotemporal spikes more during drowsiness and sleep. Carbamazepine and Valproate are useful as initial monotherapy. Treatment beyond the age of 14–16 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 aonic, atypical absence, tonic, focal, as well as generalized tonic-clonic seizures. Seizure onset around 3–5 years of age. LGS syndrome patients can have preceding infantile spasms. EEG shows a characteristic slow generalized spike and wave pattern $<$2.5Hz. Treatment options are topiramate, Levetriacetam, lamotrigine, clobazam, and Rufinamide. 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 with boys compared to girls. 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 onset of regression. Eventually, seizures tend to resolve more than the regression. Sodium channel AED (PHT, CBZ, PB, OXC) should be avoided in these patients.

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 18 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 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 offer 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 medication should be avoided in these cases as it 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, any head injury with loss of consciousness, and any history of meiningitis 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 several 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 is important to note any external signs of trauma; a good cognitive exam is important to see if there is any associated cognitive deficit. 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 increase in the T-2 signal in the hippocampus. CT Head is done in the emergency department essentially to rule out a bleed or other obvious abnormalities.

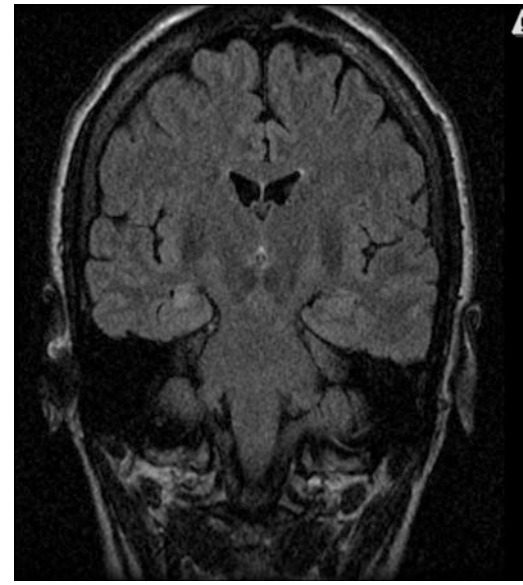

Fig. 2 MRI brain coronal FLAIR – left Mesial Temporal Sclerosis – increased T2 signal

Every seizure patient should get an MRI Brain and an EEG (Figs. 2 and 3).

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. It can show focal epileptic discharges suggestive of focal epilepsy or it can show generalized (diffuse) epileptiform discharges diagnostic of generalized epilepsy. 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

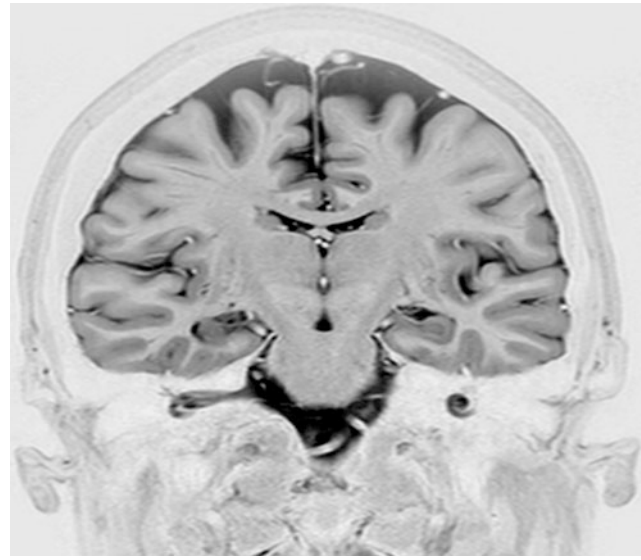

Fig. 3 MRI brain coronal view – left Mesial Temporal Sclerosis – hippocampal atrophy

definite epilepsy. Repeating the EEG does increase the yield in cases of epilepsy (Figs. 4, 5, and 6).

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 1 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 a 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 a MEG scan.

Medical Treatment

Medications are the mainstay for the treatment of epilepsy [6]. Approximately 70 % of epilepsy patients can be treated by antiepileptic drugs (AEDs). There has been an increase in the number of medications available for the treatment of epilepsy in the last two decades.

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 (Table 1).

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.

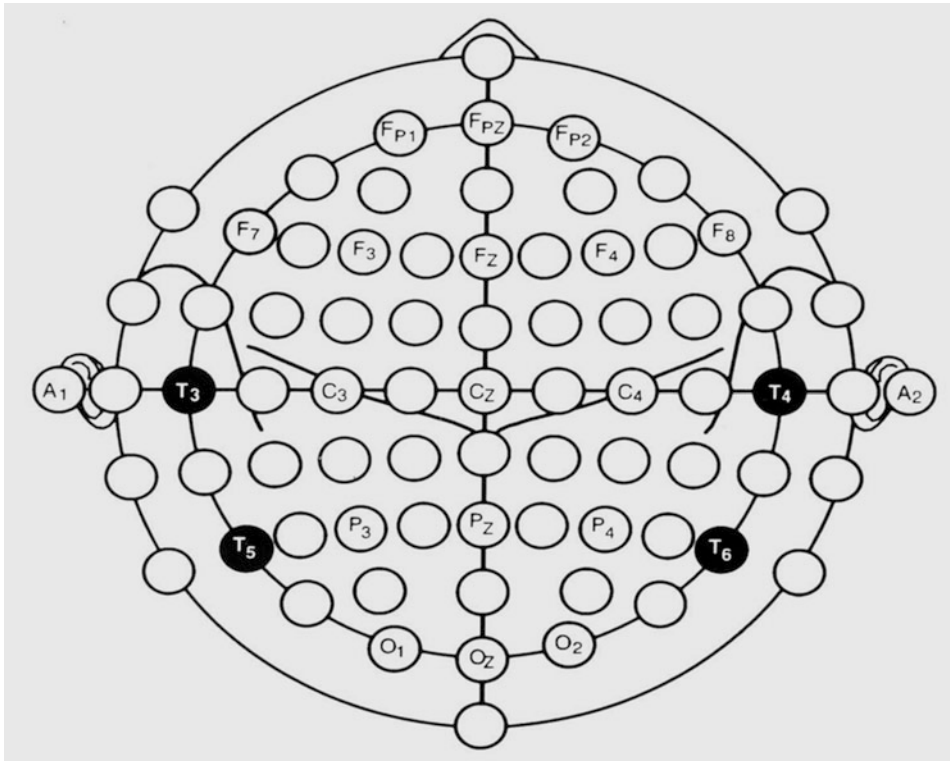

Fig. 4 EEG – recording electrodes

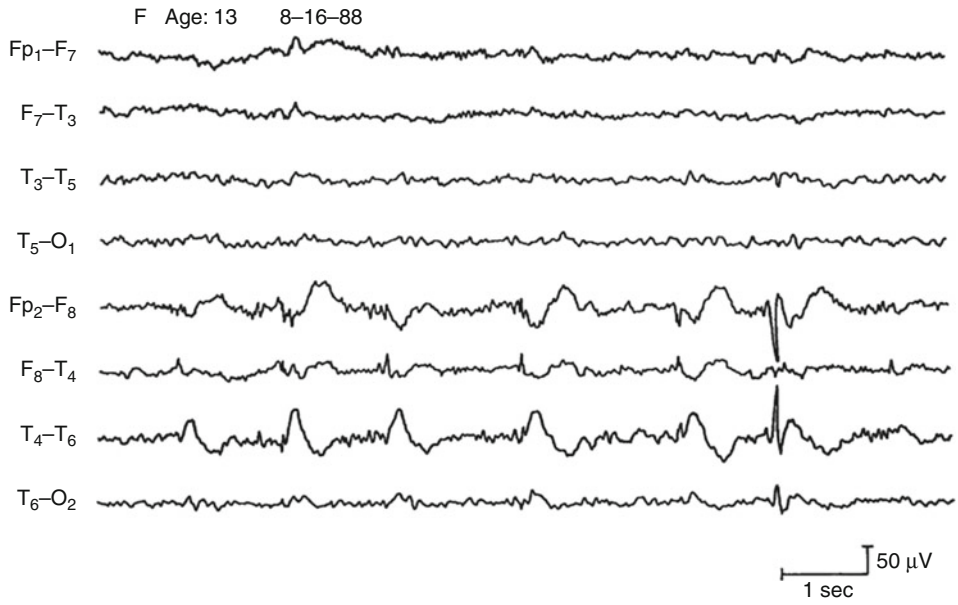

Fig. 5 EEG - Focal epileptiform discharge – right temporal spike

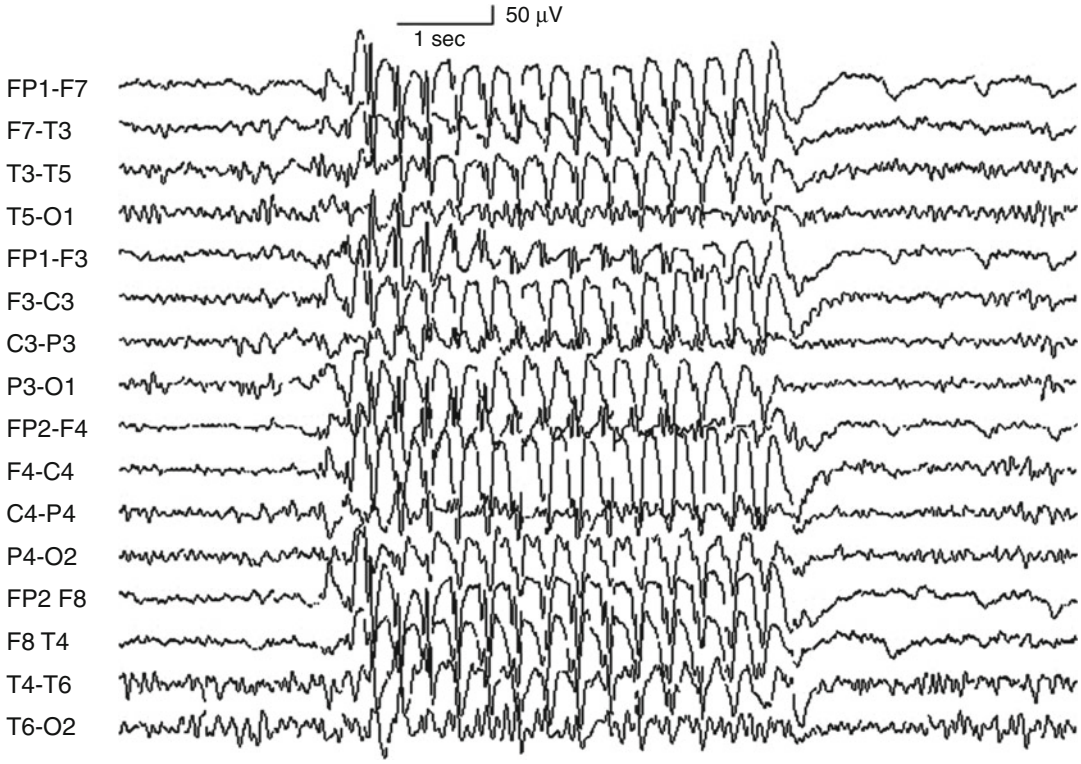

Fig. 6 EEG - Generalized epileptiform discharges – 3 Hz spike and wave discharge

Epilepsy Surgery

When patients do not respond to medications then they are candidates for respective epilepsy surgery if there is 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.

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, and the stimulation parameters can be managed externally by a programming wand and a computer via radiofrequency signals.

Status Epilepticus

Status epilepticus is a life-threatening emergency requiring immediate medical attention and affects 65,000–150,000 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 20 % mortality in status epilepticus.

The definition of status epilepticus is having continuous seizure activity for more than 30 min or two or more sequential seizures without recovery of consciousness to baseline. However, with the need for prompt care of patients there is an operational definition that is used for management

Table 1 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 eizures, 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 and generalized seizures	None	Irritability/behavior change
Topiramate	Focal and 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, dry mouth, edema, blurred vision, weight gain, 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, and shakiness
Perampanel	Focal 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 U.S.A. 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
Rufinamide	As adjunctive treatment of seizures associated with Lennox-Gastaut syndrome	Multi-organ hypersensitivity, rufinamide has been known to shorten the QT interval	Headache, dizziness, fatigue, somnolence, and nausea

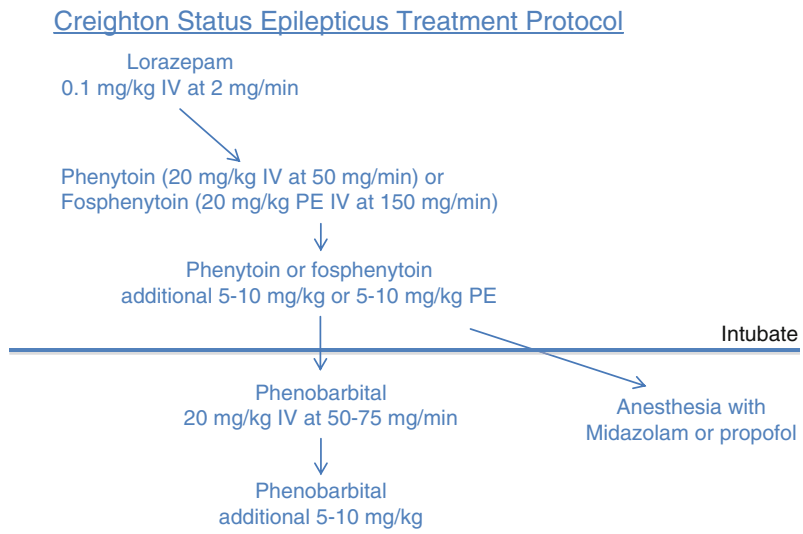

Fig. 7 Creighton Status Epilepticus Treatment Protocol

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 our status epilepticus protocol [8]. 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 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 may be in nonconvulsive status epilepticus or after paralyzing the patient for intubation this is the only way we can find out about seizure activity (Fig. 7).

Specific Conditions

Sudden, Unexplained Death in Epilepsy (SUDEP)

Sudden *nexpected* 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 1 death per 1,000 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.

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)

First Seizure

The risk of recurrence after a first seizure is about 33 % without any testing. If both the MRI Brain 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
3. Labs – complete blood counts, complete metabolic panel and urine drug screen
4. Rule out mimics
5. Syncope
6. Hyperventilation
7. Panic attack
8. Psychogenic seizure
9. Transient ischemic attack
10. Transient global amnesia
11. Migraine equivalents
12. Imaging – MRI brain with and without contrast (preferable) or CT head with and without contrast
13. EEG – higher yield with sleep deprived EEG

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Cerebrovascular Disease

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Contents

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General Principles

Definition/Background

Cerebrovascular disease refers to the group of conditions that lead to neurological deficits secondary to impairment of circulation of blood in the brain. If the brain is deprived of blood flow for longer than a few seconds, brain cells can die causing permanent brain damage leading to neurological deficits. In this chapter we will use the word "stroke" interchangeably with "cerebrovascular disease."

Stroke is the fourth leading cause of death in US adult population; it is also one of the leading causes of disability among US adult population [1, 2]. Each year 795,000 people in USA suffer from stroke resulting in a total of 6.8 million stroke survivors [1]. In 2011, stroke was responsible for 128,932 deaths in the USA, which is 41.4 deaths for every 100,000 people in USA that year [2].

In a report published by Centers for Disease Control and Prevention (CDC), elderly African American individuals with low level of education and residing in southeastern USA were found to have a higher prevalence of stroke when compared to other areas [3]. Behavioral Risk Factor Surveillance System (BRFSS) data from 2012 illustrates prevalence of stroke among different race/ethnicity as follows: 1.8 % in Hispanics, 1.9 % in Asian-Pacific Islanders, 3 % in non-Hispanic whites, 3.8 % in non-Hispanic

blacks, 4.1 % in multiracial people, and 5.8 % in American Indians/Alaska natives [3].

World Health Organization (WHO) reports stroke as the fourth leading cause of deaths among low-income countries, and globally it is the second leading cause of deaths taking toll of 6.7 million people in 2012 alone [4].

Pathogenesis

The mechanisms leading to impairment of circulation of blood in various areas of the brain can be broadly classified into two types: ischemic and hemorrhagic.

Ischemic

Ischemic stroke is caused by inadequate circulation of the blood to the brain and accounts for more than 80 % of all strokes. The aftermath of such inadequate circulation is dependent on the presence of collateral blood vessels, degree of blockage, vasculature of the patient, and blood pressure. If the blood circulation can be restored in time before the affected brain tissue dies, it is called transient ischemic attack (TIA). If the circulation cannot be restored in time, then tissue at the center of ischemia dies, but surrounding tissue with ischemia, also known as penumbra, can still be revived if circulation can be restored promptly. Hence treatment goal is directed toward early re-establishment of the circulation in the affected area.

Etiology of ischemic stroke or TIA can be grouped into three broad categories:

(a) Blockage of intracranial vessel from embolus released from a distant site, for example, embolus from heart in case of arrhythmia or valvular heart disease
(b) Thrombus formation in intracranial blood vessel
(c) Hypoperfusion due to narrowing of major extra/intracranial vessel such as carotid stenosis or hypoperfusion due to cardiac arrest. Such hypoperfusion can lead to a type of ischemia called "watershed ischemia" where the areas of brain in border zone without collateral circulation are affected

Blockage in smaller intracranial arteries can lead to ischemia in a limited brain area leading to specific deficits; such strokes are called lacunar strokes.

Hemorrhagic

This accounts for about 20 % of all strokes. As the name implies, in hemorrhagic stroke there is excess blood in intracranial space due to rupture of blood vessel(s). The possible mechanisms by which hemorrhagic stroke affects neurological function are bleeding impairing perfusion to brain tissue, mass effect due to the hemorrhage, and cytotoxic swelling around the area affected by the stroke.

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 tissue, and in SAH blood vessels rupture and bleeding occurs in subarachnoid space.

Risk Factors

Risk factors in relation to pathogenesis of stroke can be grouped as modifiable, potentially modifiable, and nonmodifiable risk factors [5, 6].

Modifiable risk factors include smoking, poor diet (high portion of red meat, organ meat, eggs, fried foods, salty snacks), physical inactivity, excess alcohol consumption, and illicit drug use [5, 6].

Potentially modifiable risk factors include psychosocial stress, depression, diabetes, dyslipidemia, heart disease, chronic kidney diseases, sleep apnea, obesity, and hypertension [5, 6].

Nonmodifiable risk factors comprise of increasing age, susceptible family history, and genetics [5, 6].

Prevention of Cerebrovascular Disease

Prevention of cerebrovascular disease can be discussed under three broad stages: primary prevention, secondary prevention, and tertiary prevention.

Table 1 Primary prevention strategies for cerebrovascular diseases [5]

Primary prevention of cerebrovascular disease
1. Take family history of stroke and appropriate counseling for risks
2. Non-invasive screening for un-ruptured intracranial aneurysms for: (a) People who have 2 or more than 2 first degree relatives with subarachnoid hemorrhage (SAH) or intracranial aneurysm (b) Similar screening for those with autosomal-dominant polycystic kidney disease (PCKD); or one or more first degree relative(s) with autosomal-dominant PCKD and SAH/intracranial aneurysm (c) Patients with cervical fibromuscular dysplasia
3. Routine physical activity
4. Lifestyle modifications and treatment with statins to reduce risk of atherosclerotic cardiovascular disease (ASCVD)
5. Lifestyle modifications (Diet and exercise) for patients with hypertension
6. Annual screening of blood pressure
7. Appropriate follow ups in patients with hypertension to maintain blood pressure less than 140 systolic and 90 diastolic
8. Maintaining body mass index (BMI) at normal range
9. Close follow up on patients with diabetes to maintain normal blood sugar, normal blood pressure and statin therapy
10. Smoking cessation
11. For patients with atrial fibrillation evaluate the need for oral anticoagulation and treat accordingly
12. Appropriate anticoagulation treatment in patients with valvular heart disease
13. Aspirin and statins should be prescribed in patients with asymptomatic carotid stenosis. For those patients undergoing carotid endarterectomy (CEA), aspirin treatment is recommended preoperatively and postoperatively unless contraindicated
14. Treatment of carotid stenosis if indicated
15. Appropriate referral for patient with sickle cell disease for prevention of stroke
16. Counseling against unhealthy alcohol drinking
17. Address illicit drug abuse
18. Identifying patients with sleep apnea and their appropriate treatment
19. Consider Aspirin 81 mg tablet daily for prevention of stroke in patients whose cardiovascular risk is more than 10 % in 10 years; female with diabetes mellitus; and in patients with chronic kidney disease.

Primary prevention includes measures to prevent development of cerebrovascular disease in those patients who do not have the disease. Table 1 summarizes key components in primary prevention of cerebrovascular disease.

Secondary prevention includes measures in management of patients with cerebrovascular disease. The following sections of this chapter discuss this stage of prevention in more depth.

Tertiary prevention involves the strategy of rehabilitation once patient has had events of cerebrovascular disease. This is discussed later in this chapter.

Approach to Patients with Stroke

The initial important steps in approach to patients with stroke are prompt recognition of signs and symptoms of stroke: initiation of stroke chain, prompt transport of the patient to appropriate center.

American Stroke Association (ASA)'s website has simplified information for public including health care professionals on prompt recognition of symptoms and signs of stroke [7]. One should be concerned for possible stroke if they recognize five symptoms and signs in patients also known as "five suddens": sudden weakness and/or numbness of one part of the body; sudden confusion and trouble communicating; sudden imbalance; sudden unknown cause of severe headache; and sudden vision impairment [7, 8]. Another approach is to remember the acronym "F.A.S.T." which means to recognize ***facial drooping***, ***arm weakness***, ***speech impairment*** as possible stroke symptoms, and if present then it is ***time to call*** for help by calling emergency medical services (EMS) [7, 8]. Only half of the patients who experience a stroke reach the hospital via EMS service; this leads to a longer delay in the stroke treatment and potentially leads to morbidity and mortality [9]. Public awareness can improve this part of the stroke chain by emphasizing a need to promptly call EMS for evaluation of stroke in suspected patients [9].

American Heart Association (AHA) and the ASA recommend stroke chain of survival which starts with early identification of warning signs of stroke and call for help; quick dispatch of EMS; quick transportation and communication to the

hospital; and rapid diagnosis and treatment. The goal of this process is to minimize nervous tissue damage and to maximize recovery of stroke patients.

The principle of management of stroke patients preceding the hospital visit is to provide support to airway, breathing, and circulation as a part of adult cardiovascular life support (ACLS) program [10]. Prehospital measures in patients with suspected stroke are oxygen supplementation, fluid administration in patients with hypotension, and hypoglycemia management if hypoglycemia is present [8, 10]. There is no evidence to support benefit of managing hypertension as prehospital management of stroke [10].

During transportation and upon arrival in a treating center, a thorough past medical history, medication history, and social history have to be gathered without delaying the triage process and urgent treatment. Acquiring the medical history will assist in differentiating the stroke from other potential differential diagnoses such as hypoglycemia, seizure disorder, psychosomatic disorder, migraine, delirium, alcohol and substance abuse, movement disorder, cranial nerve palsy, or central nervous system neoplasm [8, 11].

Examination of airway patency, breathing movements, hemodynamic status, and detailed neurological examination as well as cardiovascular examination (including examination of carotid bruit, distal pulses) and signs of coagulopathy all goes hand in hand while taking history [8, 12]. 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. The National Institutes of Health Stroke Scale (NIHSS) is a helpful tool to be used by healthcare professionals to assess patients with stroke symptoms and its severity [2]. NIHSS scale takes into account different patients' status score based on their level of consciousness, answer to orientation, response to commands, gaze, visual fields, facial movement, motor function of arm, motor function of leg, limb ataxia, sensory exam status, language, articulation, and inattention. For details on the scale, please refer to the NIHSS website [2].

Neuroimaging is the cornerstone of management of stroke and helps to classify stroke into ischemic or hemorrhagic category. It is critical to confirm ischemic versus hemorrhagic pathogenesis 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.

Before further discussion on the choice of neuroimaging, it may be relevant to discuss guidelines from "Proceedings of a National Symposium on Rapid Identification and Treatment of Acute Stroke in 1996" for any patient with stroke [13]:

(a) Physician evaluation should be done in $\leq$10 min of arrival.
(b) Stroke team should be able to see patient in $\leq$15 min of arrival.
(c) CT evaluation should be initiated in $\leq$25 min of arrival.
(d) CT interpretation should be done in $\leq$45 min of arrival.
(e) Administration of thrombolysis for stroke if indicated should be done in $\leq$60 min.
(f) Admission to appropriate inpatient setting should be done in $\leq$3 h of arrival [13].

With advances in imaging, there are now different options available for neuroimaging. The choice of neuroimaging depends on the availability of the machine/system and the condition of the patient. CT scan is similar to MRI in detecting acute intracranial hemorrhage. The sensitivity of CT and MRI scan of brain is 26 % and 83 % respectively in any acute stroke within the first 24 h of onset of symptoms [14]. Diffusion weighted MRI is found to be more sensitive to detect acute stroke even in subtle cases. MRI also helps to differentiate acute from chronic hemorrhage [14]. 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 [8]. Contrast enhanced CT and MRI provides specific information on area of brain damage, but this information was not beneficial in a study

looking at ischemic strokes [15]. Magnetic resonance angiography (MRA) has shown promise in detailing vessels involved in stroke. Computed tomographic angiography (CTA) is more rapid technique than MRA, but effects of radiation and contrast have to be considered.

Besides neuroimaging a workup of stroke includes basic metabolic panel, blood glucose, oxygen saturation monitoring, blood alcohol level, urine drug screen, cardiac enzymes, bleeding profile, electrocardiogram, and cardiac monitoring, [8, 12]. Persistent hyperglycemia has been associated with bad prognosis in all types of stroke, and management should be targeted to maintain normoglycemia as per AHA/ASA guidelines [8, 12, 16].

A comprehensive stroke center is recommended for care of patients with stroke. A comprehensive center is a multidisciplinary team that includes [17–19]

(a) Incorporation of rehabilitation services like occupational therapy, physical therapy, speech therapy, behavioral therapy
(b) Monitoring of common infections like pneumonia or urinary tract infections
(c) Speech therapist service to monitor swallowing function
(d) Appropriate interventions for feeding in patients with dysphagia
(e) Measures for prevention of future strokes
(f) Prevention of pressure sores, deep venous thrombosis (DVT), pulmonary embolism (PE), pneumonia
(g) Avoiding falls
(h) Prevention of peptic ulcers secondary to patient's prolonged intensive care unit stay or hospital stay

Comprehensive care also deals with management of possible aftermath of stroke. Management of complications of stroke needs evaluation by a team comprising of neurologists, interventional neurologists, neurosurgeons, as well as nursing staffs, rehabilitation staffs, and palliative care team trained in stroke care.

The following section in this chapter will give an overview of management based on specific pathogenesis.

Ischemic Strokes and Transient Ischemic Attacks (TIAs)

Transient Ischemic Attacks (TIAs):

TIAs are classically defined as a sudden onset of neurological weakness lasting less than 24 h. With advances in neuroimaging, TIAs are now defined as those ischemic insults where the affected tissue has not reached the stage of infarction making the neurological deficits only transient [20, 21]. However, it is important to state here that 10.5 % of patients with TIAs are found to have stroke within 90 days; this risk is 50-fold higher than patients without TIA sustaining ischemic stroke in similar age-groups [22, 23]. Half of all the strokes that followed TIAs happened within 2 days of the onset of TIAs [23]. Early treatment, however, has been associated with decrease in stroke risk in TIA by 80 % [24]. Therefore, approach to the patient with TIAs should include a thorough evaluation and identifying those groups of patients where the risk of stroke after TIAs is high [21, 23]. Higher risk of stroke after TIAs are observed in patients aged 60 and above, presence of diabetes, symptomatic speech or motor deficits, and in those patients with TIAs lasting more than 10 min [21, 23]. Because of only brief periods of neurological deficit, patients with TIAs usually present at an outpatient setting or urgent care setting instead of emergency centers. Neuroimaging should be obtained within 24 h of onset of symptoms; preferably with an MRI. A noninvasive imaging of cerebral vessels should be done as a part of routine evaluation [8, 21, 23]. There should be low threshold for hospital admission in patients with unreliable outpatient follow-ups for proper evaluation and monitoring [8, 21, 23].

Ischemic Stroke:

Under this heading are those ischemic attacks in brain where the neurological symptoms do not resolve within 24 h of onset and an evidence of infarction can be seen in neuroradiological investigations. Time to intervention from the onset of

symptoms is very critical in pathogenesis, management, and most importantly the outcome of ischemic stroke. Each minute of ischemia leads to death of 1.9 million neurons in the brain [25].

Diffusion weighted MRI is the preferred imaging compared to standard MRI and noncontrast CT scan, as diffusion weighted MRI has higher sensitivity and specificity to detect ischemia within minutes of the occurrence of initial symptoms [26]. In a study by Fiebach et al., sensitivity of detection of infarction with diffusion gated MRI was 91 % compared to 61 % with noncontrast CT scan [27]. Other imaging procedures like CT angiogram, MR angiogram, transcranial Doppler ultrasound, and conventional angiogram can also be utilized based on individual cases to identify intracranial vasculature involved [8]. In addition, extracranial vasculature study like carotid Doppler ultrasound, CT angiogram, MR angiogram, and conventional angiogram are important to find out the etiology of ischemic events. Extracranial vasculature study is useful for clinical decisions for neurology interventions such as carotid endarterectomy, angioplasty, and stenting [8]. Intracranial vasculature studies are vital to decide on procedures like mechanical thrombectomy or intra-arterial fibrinolytic therapy.

Managing Hypertension in Patients with Acute Ischemic Stroke

Thrombolytic treatment is contraindicated in patients with sustained systolic blood pressure (SBP) of more than 185 mmHg and sustained diastolic blood pressure (DBP) of more than 110 mmHg [8]. In such situations, blood pressure should be stabilized below 180 mmHg SBP and below 105 mmHg DBP before, during, and at least 24 h after thrombolysis. If a patient is not a candidate for thrombolysis, then blood pressure may be lowered if SBP is more than 220 mmHg or DBP is more than 120 mmHg. Any antihypertensive treatment has to be targeted to lower blood pressure approximately 15 % of baseline blood pressure during first 24 h after onset of symptoms of ischemic stroke.

Fibrinolysis

Fibrinolytic agents initiate local fibrinolysis/breakdown of the blood clot in the area where cerebral blood circulation has been blocked, resulting in recovery of cerebral circulation.

Eligible candidates for such fibrinolysis are those patients who are 18 years or older in age, who present with measurable neurological deficits within 3 h of onset of symptoms [8]. Indication is now extended from 3 to 4.5 h from onset of symptoms with the exception of patients aged 80 years and above, severe stroke (with NIHSS more than 25), taking oral anticoagulants regardless of INR, and patients with a history of diabetes and prior ischemic stroke. *Extent of ischemia in imaging is not an important factor for initiation of fibrinolytic therapy.*

Following patients are absolutely contraindicated for fibrinolysis treatment:

1. Significant head trauma or stroke within 3 months prior to stroke symptoms
2. Subarachnoid hemorrhage
3. Arterial injury in noncompressible part of the body within a week
4. Prior history of intracranial hemorrhage
5. Intracranial tumor and vascular malformations
6. SBP $>$ 185 mmHg; DBP $>$ 110 mmHg
7. Active internal bleeding
8. High bleeding risks like platelet count $<$ 100,000/mm^3, elevated aPTT $>$40 s, INR $>$1.7, PT $>$15 s, use of anticoagulants, thrombin inhibitors, etc.
9. Hypoglycemia with blood glucose $<$ 50 mg/dl
10. CT scan showing large hypodensity covering more than a third of cerebral hemisphere

CT scan evidence of hypodensity and mass effect when treated with fibrinolytic agent is found to be associated with eightfold higher risk for intracranial hemorrhage [8, 28].

Following situations are relative contraindications, where clinical decision is made on an individual basis [8]:

(a) Pregnancy
(b) Seizure at onset of symptoms
(c) Major surgery or serious trauma within 2 weeks
(d) Urinary tract or gastrointestinal bleeding within 3 weeks
(e) Acute MI within 3 months
(f) Rapidly improving stroke symptoms

Food and Drug Administration (FDA) approved intravenous recombinant tissue plasminogen activator (rTPA) as a fibrinolytic agent for use in acute ischemic stroke in 1996. The treating dose is 0.9 mg/kg (total dose not exceeding 90 mg) over 60 min [29]. The bolus dose is administered as 10 % of the total dose over 1 min.

Patient should be closely monitored in stroke unit or intensive care unit during and throughout the management. Throughout the treatment and monitoring period patient's blood pressure and neurological exam should be assessed every 15 min for first 2 h. Follow-up neuroimaging is done after 24 h of treatment. The treatment should be discontinued if patient exhibits severe headache, if blood pressure rises acutely, or if patients develop nausea, vomiting, and worsening of neurological weakness. Urgent neuroimaging has to be performed in event of such concerning symptoms.

Other Agents

Streptokinase is not recommended anymore due to its higher risks with intracranial hemorrhage [30]. Other newer fibrinolytic agents such as Urokinase, Desmoteplase, Reteplase, Tenecteplase have not been tested extensively [8].

Endovascular treatments are considered only in highly specialized centers and in selected patients. Such treatments include intra-arterial fibrinolysis, mechanical clot/embolus removal procedures, acute angioplasty, and stenting.

Role of thrombin inhibitors in treatment of acute ischemic stroke is not established. 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 [8].

Antiplatelet Therapy

Aspirin 325 mg is recommended for patients to take orally within 24–48 h of onset of stroke symptoms. Although role of clopidogrel in secondary prevention of ischemic stroke has been established, its role in treatment of patients with acute ischemic stroke is not well known. Furthermore during an episode of acute ischemic stroke, aspirin-clopidogrel dual therapy increases the risk of bleeding and does not improve the outcome of ischemic events compared to monotherapy alone [8, 31].

Other Considerations

Cardiac monitoring with continuous electrocardiogram should be done as soon as possible after the onset of symptoms and continued throughout the assessment and for at least 24 h upon admission [8]. Volume status should be addressed appropriately by volume replacement if indicated [8]. Hyperthermia if present should be worked up for etiology and addressed appropriately; fever in stroke patient can be a bad prognosis [8, 32]. Protective effects of hypothermia in stroke are not well established [8]. Regarding statins, continuation of statin therapy during hospitalization of patients with acute ischemic stroke is recommended. Specific treatment such as revascularization procedure is considered if there is presence of significant carotid stenosis; anticoagulation strategy is for atrial fibrillation [8].

Complications

Approximately, one fourth of the patients with ischemic stroke will develop complications. The most common complications following an ischemic stroke are (with incidence in parenthesis): brain edema (33 %), intracranial hemorrhage

(10 %), recurrent ischemia (11 %), and seizures (<10 %). Brain edema can increase intracranial pressure leading to further neurological weaknesses and increases the risk of mortality. Such complication from brain swelling usually occurs within 3 days of stroke. Hence, close monitoring of patients is warranted for the first 72 h [33].

After the initial phase of management, another secondary prevention strategy has to be started along with behavioral approaches for risk modifications [34]. This includes addressing key modifiable risk factors, which are control of blood pressure and diabetes mellitus. Smoking cessation has to be reinforced [34]. Other behavioral modifications include addressing excess alcohol consumption, obesity, and physical inactivity [34]. Managing valvular heart disease, cardiac arrhythmias, and addressing symptomatic carotid stenosis are important [34]. With regard to antiplatelet therapy any of the following options are recommended [34]:

(a) Aspirin (50–325 mg daily orally)
(b) Combination of aspirin (25 mg) and extended-release dipyridamole (200 mg) twice daily
(c) Clopidogrel (75 mg daily orally)

Combination of aspirin and clopidogrel has not been found to be beneficial and appears to have higher bleeding risks. In ischemic strokes secondary to carotid stenosis of 55–99 %, treatment with aspirin 325 mg daily orally is recommended [34].

Treatment of sleep apnea in patients with obstructive sleep apnea and ischemic strokes has been shown to improve outcomes [34].

Within the context of secondary prevention it is relevant to discuss the new guidelines on management of cholesterol to prevent atherosclerotic cardiovascular dfisease (ASCVD) published jointly by American Heart Association (AHA) and American College of Cardiology (ACC) in 2013 [35]. ASCVD includes acute coronary syndrome, history of myocardial infarction, angina, peripheral artery disease, stroke, and transient ischemic attack. Four groups of patients are found to benefit from therapy with statins:

(a) Patients with any form of clinical ASCVD
(b) Patients at age 40–75 with LDL-cholesterol at level 190 mg/dl or greater
(c) Patients at 40–75 years of age with diabetes and LDL-C between 70–189 mg/dl
(d) Patients 40–75 years of age without diabetes but whose estimated 10 year ASCVD risk is 7.5 % or greater

Taking the risks of ASCVD in consideration, these groups of patients will benefit from high-intensity statins or moderate-intensity statins in elderly at or more than 75 years of age. The proposed new 10 year ASCVD risk calculator takes into account gender, age, presence or absence of diabetes mellitus, SBP reading, presence or absence of hypertension treatment, smoking status, and total and HDL cholesterol [35].

Intracerebral Hemorrhage (ICH):

One in every ten patients with stroke is due to intracerebral hemorrhage (ICH) [2, 36–38]. Approximately a third of all patients with ICH die within a month; 50 % of all such deaths are within the first 48 h [36, 38]. Compared to ischemic strokes, ICH symptoms progress more rapidly, over minutes to hours. Some of the key symptoms of ICH are sudden headache, nausea, vomiting, elevated blood pressure, altered level of consciousness, and focal neurological deficits [39]. History of intake of medications that predispose to bleeding (like antiplatelet, antithrombotic agents) and other medical conditions that can lead to bleeding (like liver disease) are very important [12].

Prompt recognition of the ICH and its prognostic indicators will guide the management and prompt referral to a tertiary facility if necessary [12]. Volume of ICH and admission Glasgow coma scale (GCS) of the patients are strong prognostic indicators for patients with ICH [37]. High volume of ICH, low GCS, and presence of hydrocephalus are associated with bad prognosis [37, 40]. Another poor prognostic factor after hemorrhagic stroke is presence of fever within the first

3 days of stroke. Fever in the patient with ICH has been associated with supratentorial ICH and ventricular hemorrhage [41]. Low fibrinogen level, cortical location of ICH, and milder extent of neurological deficits are associated with better prognosis [42].

Patients with hemorrhagic stroke are found to be sicker than ischemic stroke patients. They also need close monitoring of intracranial pressure and neurological functions. They also have higher need for neurosurgical interventions [12].

Head CT scan and MRI of the brain are equally good in detecting ICH. Compared to serial MRIs, serial head CT scans are more feasible to monitor blossoming of the intracranial hemorrhage. MRI of the brain is superior in identifying vascular malformations. Cerebral angiography is indicated if there is bleeding in unusual sites like sylvian fissure bleeds, vascular abnormalities, subarachnoid hemorrhage, abnormal calcifications, or if no obvious etiology of hemorrhage can be identified [12]. Timing of angiography has to be weighed against hemodynamic stability of patients; unstable patients may need prompt neurosurgical intervention prior to angiography [12].

The key treatment goals in patients with ICH are to stop the bleeding, to remove the hematoma, and to address problems due to mass effect of the hematoma [12]. Just like in the case of ischemic stroke, the patient's airway patency, breathing motion/movements, and hemodynamic stability have to be addressed before specific management is initiated. If the treating center does not have a neurosurgical service, a timely referral to tertiary center can improve the outcome after a hemorrhagic stroke. Intensive care monitoring is needed throughout the recuperation process. ICU monitoring includes close monitoring of the hemodynamic status, intracranial pressure (ICP), cerebral perfusion pressure (CPP),, neurological status examination, and assessment of seizures [12]. Antiseizure medicines can be used prophylactically especially in patients with lobar hemorrhage. Duration of such prophylaxis should be brief unless there is a change in clinical picture of the patient. Use of recombinant activated factor VII (rVIIa) in patients with hemophilia has been proven to be beneficial, but its use for the treatment of bleeding in patients without coagulopathy has not been well established. The standard goal for blood pressure management in patients with ICH varies according to the patient's baseline blood pressure, history of hypertension, degree of intracranial pressure (ICP), and patient's age among many other variables [12]. Rehabilitation is started as soon as the patient is stable for mobilization.

Managing High Blood Pressure in Patients with ICH

The strategy of addressing high blood pressure differs among patients with ICH and patients with ischemic stroke. The outline of management of high blood pressure in ICH patients is recommended as follows [12]:

(a) If SBP >200 mmHg or mean arterial pressure (MAP)>150 mmHg, aggressive lowering of blood pressure is recommended to decrease risk of more hemorrhage.
(b) If SBP >180 mmHg or MAP >130 mmHg, ICP may be elevated; in such situation ICP monitoring and lowering blood pressure is important to maintain CPP between 60 and 80 mmHg.
(c) If SBP >180 mmHg or MAP >130 mmHg without any evidence of elevated ICP, a gradual blood pressure lowering should be the strategy with target blood pressure of 160/90 mmHg.
(d) In patients with SBP of 150–220 mmHg, the target SBP of 140 is probably safe.

There is high risk of increased ICP in patients with ICH due to multiple mechanisms like mass effect, swelling secondary to ischemia, secondary hemorrhage, and hydrocephalus [43]. Clinically patients with elevated ICP should be monitored closely with the help of tools like NIHSS scale and GCS; patient's ICP and CPP should be monitored in the intensive care unit. ICP lowering strategies used in intensive care units are elevation of head of bed to 30°; drainage of cerebrospinal fluid; osmotic therapy (mannitol, hypertonic

saline), and hyperventilation [12]. In patients with hydrocephalus of worsening neurological symptoms, ventricular drainage of cerebrospinal fluid can be considered [12].

Neurosurgical intervention to remove hematoma is recommended in patients with ICH > 3 cm, with deterioration of clinical situation, brainstem compression signs, or hydrocephalus leading to obstruction of CSF flow [12]. In supratentorial ICH with lobar clot within 1 cm of the surface of brain, evacuation can be considered. The time to craniotomy and evacuation of the clot has to be managed perfectly as there is possible harm due to recurrent bleeding in case of early craniotomy and there is the possibility of minimal benefit in outcome with added risks of surgery with late craniotomy [12].

In patients with ICH and impaired mobility, there is a high risk of development of DVT and PE. Pneumatic compression of legs is recommended for prevention of DVT. Only after cessation of intracranial bleeding, cautious use of anticoagulants as prophylaxis for thromboembolism can be considered, which is usually after 3–4 days of ICH. In cases with high bleeding risk, inferior vena cava (IVC) filter placement is widely used to prevent progression of DVT to PE [12].

The recurrence of ICH depends on the risk factors for ICH. The odds ratio for recurrence of ICH in elderly patients > 65 years of age and male gender are 2.8 and 1.8 times respectively [44]. The odds ratio of ICH recurrence in patients with untreated hypertension and treated hypertension are 3.5 and 1.4 respectively [45]. Relationship between smoking, heavy alcohol use, cocaine use, and ICH are well established, and these risk factors need to be addressed for prevention of ICH and its recurrence [12].

Subarachnoid Hemorrhage (SAH):

Three percent of all stroke is due to SAH [1]. SAH due to rupture of aneurysm is also called aneurysmal SAH (aSAH) and accounts for 85 % of SAH.

Fifteen percent are nonaneurysmal SAH (NASAH) [46]. Nonaneurysmal bleeding causes are often not identified. Some of the causes are perimesencephalic nonaneurysmal hemorrhage and other nonaneurysmal vascular malformations. Perimesencephalic nonaneurysmal bleed has excellent prognosis compared to aneurysmal bleeds [46].

Nonmodifiable risk factors for aSAH are presence of cerebral aneurysms, female gender, history of prior aneurysmal bleed, family history of cerebral aneurysms [16]. Modifiable risk factors for aneurysmal SAH are smoking, hypertension, cocaine use, alcohol abuse [16]. Smoking cessation, cutting down alcohol, treatment of hypertension, and diet rich in vegetables may prevent incidence of SAH [16]. For first-degree relative of patient with familial aneurysmal SAH or history of aneurysmal SAH, a noninvasive test to screen for aneurysms can be considered [16]. Among cerebral aneurysms, those that are large, located at posterior communicating artery (PCA), or the vertebrobasillary system aneurysms are at higher risk of developing aneurysmal SAH [16]. Although aneurysmal size of more than 7 mm size of aneurysm is more prone to develop SAH [47], risk factors like smoking, alcohol, and psychosocial stress can influence the rupture of aneurysm regardless of the size [48, 49].

There is a high risk of early rebleeding of aneurysms, therefore any case of aneurysmal SAH should be closely monitored and re-evaluated after treatment with routine reimaging [16]. Furthermore after discharge, these patients should be followed up closely with regard to minimizing risk factors and behavioral modifications [16].

SAH should be the primary diagnosis of any patient who presents with acute sudden severe headache unless proven otherwise [16]. Most SAH will be diagnosed with a noncontrast head CT. If the initial noncontrast CT scan is inconclusive an evaluation of cerebrospinal fluid after lumbar puncture will help with the diagnosis. Other imaging modalities that can be considered are CT angiography, digital subtraction angiogram (DSA), or brain MRI[16].

Surgical method is the primary mode of management for SAH. For majority of aneurysmal bleeds, the aneurysm should be repaired by surgical clipping or endovascular clipping as soon as possible. Preventing rebleeding is a key issue in the

management of aneurysmal bleed. Most of the rebleeding occurs within 12 h of first bleed [50]. Rebleeding associated with high blood pressure can be prevented by judicious use of antihypertensives. Although there is no established cutoff blood pressure as a treatment goal, AHA/ASA guidelines recommend maintaining the SBP under 160 mmHg based on expert consensus [16]. Limited studies have shown benefits on short-term treatment with antifibrinolytic therapy (tranexamic acid or aminocaproic acid) to reduce rebleeding in patients with high risk of repeat bleed [16, 50].

Cerebral arterial vasospasm leading to delayed cerebral ischemia (DCI) is the primary reason for disability and death after aneurysmal SAH. Controlled studies on SAH management demonstrate no benefit on outcome from traditional hemodynamic augmentation of triple-H therapy (hemodilution, hypervolemia, and hypertensive therapy) [16]. 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 [51]. The mechanism of action by which the drug prevents DCI is unknown. In a Cochrane review by Dorhout et al., Nimodipine was found to prevent arterial vasospasm and DCI [51]. Hemodynamic stability by maintaining normal volume status of the body is also recommended to prevent DCI [52]. SAH associated hydrocephalus is treated by draining excess cerebrospinal fluid either by lumbar drainage or external ventricular drainage [16].

Prophylactic antiseizure medicine is recommended to prevent seizures after SAH [16].

Rehabilitation in Patients with Cerebrovascular Disease

Cerebrovascular disease is a leading cause of disability in USA. After stroke event, 40 % of patients sustain moderate disability, and about 20 % sustain severe disability affecting their daily life [53]. Organized multidisciplinary rehabilitation program has been proven to improve functional outcome of patients after stroke [28, 53, 54]. Table 2 summarizes key strategies in rehabilitation of patients with stroke.

Table 2 Tertiary prevention strategies for cerebrovascular diseases [19, 53]

Strategies in rehabilitation
1. Use standardized tool like NIHSS for close monitoring of patients
2. Swallowing screening in all patients in order to screen for dysphagia and to prevent aspiration
3. Address nutritional status of the patient to meet calorie and protein needs; use of feeding tube is recommended in case this need can be fulfilled orally
3. Prevention of DVT by appropriate strategies
4. Early mobilization of stroke patients; addressing motor impairment like spasticity
5. Multidisciplinary approach is proven to improve outcome in rehabilitation for stroke patients. This includes physical therapy, occupational therapy, speech therapy and palliative care
6. Strategies to prevent pressure ulcers
7. Address incontinence, urinary retention and constipation issues
8. Falls prevention strategies
9. Screen and manage depression, counsel patients and their families

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Movement Disorders

Connor B. McKeown and Paul Crawford

Contents

Parkinsonism/Parkinson's Disease

Idiopathic Parkinson's disease (IPD) has a prevalence of about 0.3 % in the general population with prevalence increasing to 5 % by age 85. The disease is fairly rare less than 50 years of age. Smoking appears to be a protective factor, with less smokers progressing to IPD [1].

Diagnosis

The diagnosis of IPD rests on the presence of cardinal motor symptoms – distal resting tremor (between 3 and 6 Hz), rigidity, bradykinesia, and atypical onset. In addition to this, a response to levodopa and the absence of atypical symptoms are very suggestive of the disease [2]. Atypical symptoms such as early postural instability (within 3 years of onset), early freezing phenomena, hallucinations (not due to treatment), early cognitive impairment, and paralysis of upward gaze suggest a diagnosis other than IPD. For a patient to have true Parkinsonism, some form of upper body akinesia must be present. Upper extremity rigidity is usually present, and a resting tremor is present in about two-thirds of patients [3]. Given that the prevalence of IPD increases with advanced age, it can often be misdiagnosed since patients may assume that they are just "slowing down."

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- **Akinesia:** This is the most disabling feature of IPD and is present in all cases [3], especially in the upper body. It is a compendium of symptoms that involves slowness of movement (bradykinesia), poverty of movement, difficulty initiating movement, decreased ability to initiate movements, and accomplish alternating movements. Poverty of movement involves what is commonly called the "mask facies" or staring. These manifestations are due to the inability to initiate movements. Other common complaints are weakness, fatigue, difficulty buttoning clothes, difficulty swallowing, and a soft voice. Micrographia, or small handwriting, can be a subtle sign of the development of IPD [4].
- **Tremor:** Tremor of IPD is typically a resting tremor and can be distinguished from many other conditions because it often disappears when the tremulous body part is activated. There are times when it is present during activity, but it is typically much more prevalent at rest. The typical resting tremor has a frequency between 3 and 6 Hz, though most are found to be between 4 and 5 Hz [5]. The tremor may begin in a single finger and usually progresses to the classic "pill rolling" tremor of the hand and then often involves the entire limb. With time, other extremities begin to be involved. Additionally, Parkinson's tremor may be found in the lips, tongue, and jaw [6].
- **Rigidity:** Rigidity is increased tonicity of flexor and extensor muscle groups during passive movement of a joint. This symptom is usually only manifest during physical exam and often is not appreciated by the patient. In a similar manner to tremor, it often begins unilaterally and then can progress to other extremities. There are two main types of rigidity: "lead pipe" or "cogwheeling." Lead pipe rigidity refers to smooth tonic resistance throughout passive range of motion. Cogwheel rigidity is thought to be due to tremor superimposed upon rigidity and is characterized by a pattern of resistance and relaxation as the physician moves the extremity through range of motion.
- **Gait Disturbances:** Rigidity, bradykinesia, and tremor often lead to gait disturbances as the disease progresses and the manifestations become much more diffuse. As a patient's stride shortens, their gait becomes more shuffling, and they adopt a stooped posture. Patients often have difficulty initiating ambulation and tend to lean forward involuntarily while taking very quick, short steps – sometimes on the forefoot or toes to avoid falling (festinating gait). A simple clinic test used to detect postural instability is the "pull test." After warning the patient, the examiner can stand behind the patient and pull backward on their upper arms. Those with mild instability will take a step or two backward to regain their balance, while those with severe instability will be forced to fall helplessly into the hands of the examiner. This is helpful for patients and caregivers to understand the serious potential for falls [7].

Differential Diagnosis

IPD is essentially a diagnosis of exclusion. Thus, it is important to rule out other causes of Parkinsonism in patients that are thought to have IPD. The physician should not hesitate to start a patient on anti-Parkinsonism drugs, however. In the end, if the patient fails to respond, alternative diagnoses must be sought.

- **Drug-Induced Parkinsonism:** The second most common cause of Parkinsonism is drug-induced Parkinsonism (DIP). Clinical features of DIP usually include a bilateral and symmetrical Parkinsonism. Bradykinesia and rigidity are often more prominent than in IPD. Clinical features alone cannot be used to differentiate IPD from DIP. When a patient presents with symptoms of Parkinsonism, a careful review of medications should be undertaken to reveal any common causes of DIP. Common offenders include antipsychotics, antiemetics, calcium channel blockers, and drugs that deplete dopamine (see Table 1) [8]. In addition

Table 1 Drugs implicated in drug-induced Parkinsonism

Typical antipsychotics	Chlorpromazine, prochlorperazine, perphenazine, fluphenazine, promethazine, haloperidol, pimozide, sulpiride
Atypical antipsychotic	Risperidone, olanzapine, ziprasidone, aripiprazole, clozapine, quetiapine
Antiemetics	Metoclopramide, levosulpiride, clebopride, domperidone, itopride
Calcium-Channel blocker	Flunarizine, cinnarizine
Dopamine depleters	Reserpine, tetrabenazine
Mood stabilizer	Lithium
Antidepressant	Citalopram, fluoxetine, paroxetine, sertraline
Antiepileptic drugs	Valproic acid, phenytoin

Adapted from table in Ref. [8] with additions from Refs. [7, 9, 10]

to Parkinsonism, these drugs can cause other movement disorders such as tardive dyskinesia (TD), which is a disorder of the face that causes twisting movements of the tongue or smacking of the lips. Abnormal movements of the limbs can also occur with TD. This can persist for years and is sometimes permanent, though with early identification and discontinuation of medications, TD may improve over time [9]. DIP will usually resolve within weeks to months of stopping the offending agent; however, it may persist in 10–50 % of patients. Those with a full and lasting recovery are the only ones that are considered to have a pure DIP. Those patients with persistent Parkinsonism, and sometimes progression after withdrawing the offending agents, probably had a preclinical IPD [8] (Table 1).

- **Cerebrovascular disease:** Infarct to the area of the basal ganglia or brainstem may cause Parkinsonism. Clues that point to this etiology might include abrupt onset of symptoms as well as the presence of risk factors for cerebrovascular disease. If a patient has other neurological complaints such as paralysis, seizures, or numbness, or if focal deficits such as aphasia, abnormal reflexes, and cranial nerve deficits are appreciated, then prompt consideration of and investigation for cerebrovascular disease should be made. Additionally, space occupying lesions such as tumors or abscesses could cause similar symptoms as could hydrocephalus. Patients in whom these are a consideration should undergo advanced imaging with computed tomography (CT) or magnetic resonance imaging (MRI).
- **Inherited disease:** Several inherited disorders can present with Parkinsonism. As such, a thorough family history is important to obtain.
  - Wilson's disease is associated with copper deposition in the liver and basal ganglia. If a patient presents with Parkinsonism 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 [10].
  - Huntington's disease is an inherited disease caused by trinucleotide repeat expansion in an autosomal dominant pattern. However, Huntington's disease presenting with true Parkinsonism is fairly rare because the typical movement is choreiform, which is rapid, involuntary, nonrepetitive, or arrhythmic movements of face, trunk, or limbs https://m.youtube.com/watch?v=VZlUNLJiEhk
- **Dementia:** Patients with Alzheimer's disease often develop some signs of Parkinsonism, though they are usually mild.
  - The second most common cause of neurodegenerative dementia is dementia with Lewy bodies (DLB), which very frequently can be confused for IPD. Characterizations of this disease include visual hallucinations, fluctuating cognition, and Parkinsonism. Patients with IPD often do develop cognitive decline, though it can be distinguished from DLB because those with DLB usually develop the dementia concomitantly or before the development of Parkinsonism. In those with IPD who develop dementia, Parkinsonism is usually present for more

than a year prior to dementia onset. Additionally, hallucinations are inconsistent with IPD [11].

- Another IPD mimic is progressive supranuclear palsy (PSP). It can cause a frontal lobe dementia, although that can take several years to develop. Otherwise, it can be differentiated from IPD by vertical supranuclear palsy with downward gaze. It has a poor prognosis as death occurs at a median of 6 years after onset with progressive decline. It can be difficult to distinguish from IPD as a small percentage of patients may have some initial response to levodopa [12].

Therapy

Unfortunately, there is no cure for IPD. However, drug therapy can be extremely useful in improving quality of life and controlling some of the debilitating symptoms associated with Parkinsonism, and it is the mainstay of treatment for Parkinsonism. Adjuncts to drug therapy include physical therapy, occupational therapy, and counseling which can also help patients and their families cope with the disease. Additionally, a randomized controlled trial has shown improvements in spinal flexibility and physical performance following specific exercise programs aimed at those specific areas (Table 2) [13].

Table 2 Drugs used for treatment of idiopathic Parkinson's disease

Class/Agent	Starting dose	Maximum dose
Dopamine precursor		
Levodopa/carbidopa (Sinemet)	100/25 mg two to four times daily	2000/200 mg/day
Dopamine agonists		
Bromocriptine (Parlodel)	1.25 mg bid	30 mg tid
Pramipexole (Mirapex)	0.125 mg tid	1.5 mg tid
Ropinirole (Requip)	0.25 mg tid	8 mg tid
Rotigotine (Neupro)	2 mg/24 h transdermal patch	6 mg/24 h
Apomorphine	2 mg tid subcutaneous injection	20 mg/day
Monoamine oxidase B (MAO B) inhibitors		
Selegiline (Eldepryl)	2.5 mg bid	5 mg bid
Catechol-O-methyltransferase (COMT) inhibitors		
Entacapone (Comtan)	200 mg/dose	200 mg 8 x/day
Tolcapone (Tasmar)	100 mg tid	200 mg tid
Anticholinergics		
Trihexyphenidyl (Artane)	1 mg qd	10 mg qd
Benztropine (Cogentin)	0.5 mg qd	6 mg qd
Miscellaneous		
Amantadine (Symmetrel)	100–200 mg qd	200 mg

From Refs. [2, 18, 19]

- **Levodopa/Carbidopa:** Levodopa is the most effective treatment for symptomatic treatment of IPD. It especially helps with symptoms of bradykinesia but can also manage tremor and rigidity, though is less likely to help with the postural instability. Levodopa is the immediate precursor to dopamine. It is given with a decarboxylase inhibitor (carbidopa) with the intention of preventing metabolism to dopamine in the periphery, thus increasing its availability and effectiveness in the Central Nervous System (CNS). It should be initiated as soon as symptoms of IPD develop as it can aid in diagnosis (as most other causes of Parkinsonism will not respond to it), improve functional capacity, and actually improve patient survival [14]. When initiating levodopa/carbidopa, dose titration should be accomplished to find a dose that provides maximum benefit while avoiding unwanted side effects as listed in Table 3. The typical dose of levodopa for most patients will end up being between 300 and 600 mg daily. Using adjunctive medications with levodopa/carbidopa can improve patient responsiveness at lower doses and avoid unwanted side effects. As the disease progresses, responsiveness to therapy decreases.

Table 3 Side effects of commonly used medications for treatment of idiopathic Parkinson's disease

Class of medication	Side effects
Dopamine precursors	Common – Nausea, somnolence, dizziness, headache
	Less common – confusion, hallucinations, delusions, agitation, psychosis, orthostatic hypotension, hip fractures (due to elevation in serum homocysteine levels), motor fluctuations
Dopamine agonist	Common – Nausea, vomiting, sleepiness, orthostatic hypotension, confusion, hallucinations, peripheral edema
	Less common – Valvular heart disease, impulse control disorders, dopaminergic dysregulation syndrome
MAO B inhibitors	Nausea, headache, confusion, insomnia
COMT Inhibitors	Dyskinesia, hallucinations, confusion, nausea, orthostatic hypotension, diarrhea, elevated liver enzymes
Anticholinergics	Memory impairment, confusion, hallucinations, dry mouth, blurred vision, constipation, nausea, urinary retention, impaired sweating, tachycardia.
Amantadine	Livedo reticularis (mottled skin), ankle edema, confusion, hallucinations, nightmares

From Refs. [2, 9, 18]

- **Dopamine Agonists:** The most common dopamine agonists used are pramipexole, ropinirole, and bromocriptine. These may delay onset of dyskinesias or wearing off as compared to levodopa alone. However, adverse effects are common with dopamine agonists and may limit their use. Similarly to levodopa, patients should be started at a low dose and titrated slowly with close follow-up for effectiveness and side effects. When adding agonists to levodopa/carbidopa, the dose of levodopa should be titrated downward. Rotigotine is another option of dopamine agonist and may benefit those patients that cannot tolerate oral medications. It is a once daily transdermal patch. Another dopamine agonist on the market is apomorphine, which is an injectable medication that can be used as rescue injections or to treat levodopa-induced motor fluctuations. Prior to initiating its use, however, a challenge test dose must be accomplished to ensure that it is tolerated by the patient as side effects can be severe and include chest pains, severe hypotension, vomiting, and loss of consciousness. Additionally, its use with ondansetron or serotonin receptor agonists is contraindicated as it can worsen side effects [15]. All dopamine agonists must be tapered off slowly when discontinuing as abrupt withdrawal can lead to severe withdrawal symptoms [16].
- **Monoamine Oxidase B (MAO B) Inhibitors:** Selegiline delays catabolism of dopamine allowing it to work longer within the CNS. There has been some discussion on whether selegeline can also offer neuroprotection, though this has not been well established in long-term follow-up studies [17]. It is not as good for monotherapy as either levodopa/carbidopa or dopamine agonists, though if used, may delay the need to start levodopa. If using as an adjunct, the dosage of levodopa should be decreased by about 20 %.
- **Catechol-O-Methyl Transferase (COMT) Inhibitors:** COMT inhibitors are used to block the catabolism of levodopa in the gastrointestinal (GI) tract and periphery. Their effectiveness is similar to that of adding carbidopa to levodopa as it increases levodopa availability in the CNS. They have been shown to reduce motor fluctuations or the wearing-off phenomenon in those patients treated with levodopa. They are ineffective when given alone but have been shown to improve disabling complications of Parkinsonism when given with levodopa [18]. Levodopa dosage should be decreased by about 25 % to decrease dyskinesia and other levodopa-related side effects.
- **Anticholinergics:** Anticholinergics have best effect on the tremor of Parkinsonism and are most useful for those patients that have disabling tremor but are not as bothered by gait disturbance or bradykinesia.

- **Amantadine:** This is an antiviral agent found to have some effectiveness on parkinsonian symptoms. It is most often used early in the disease as an adjunct to levodopa therapy. Its mechanism of action is unknown, but it is thought to possibly increase dopamine release, inhibit dopamine reuptake, and stimulate dopamine receptors [19].

Other therapies exist beyond pharmacological management. In patients that progress to severe IPD that are not responding to typical therapies, other options should be considered. Consultation with neurologists and neurosurgeons is important as patients may undergo continuous apomorphine infusions or deep brain stimulation (DBS). A large randomized control trial showed that in select patients with advanced IPD and motor complications, DBS improved motor functions and motor fluctuations when compared to best medical therapy [20]. Stimulation generally involves the subthalamic nucleus and globus pallidus pars interna with stimulation of the subthalamic nucleus leading to greater reduction in antiparkinson medication doses, though change in motor function was not significantly different [21]. DBS has largely replaced prior surgical options such as thalamotomy and pallidotomy. It is preferred due to its proven efficacy and decreased complications. It is hoped that future research may establish improved treatments with proof of neuroprotective therapy to prevent long-term deterioration and disability.

Tremor: Other Causes

Tremor is an involuntary, rhythmic, oscillatory movement of a body part. It is the most common movement disorder encountered in clinical practice. There is no diagnostic standard to distinguish among common types of tremor, which can make the evaluation challenging. However, establishing the underlying cause is important because prognosis and specific treatment plans vary considerably. History and physical examination can provide a great deal of certainty in diagnosis. The most common tremor in patients presenting to primary care physicians is enhanced physiological tremor, followed by essential tremor and parkinsonian tremor. All tremors are more common in older age [22]. Tremors fit into classification of either action or resting (Table 4).

Table 4 Broad classification of tremor

Tremor type	Description
Action	Occurs with voluntary contraction of muscle Includes
Postural	Occurs when the body part is voluntarily maintained against gravity – includes essential, physiologic, cerebellar, dystonic, and drug-induced tremors
Kinetic	Occurs with any form of voluntary movement – includes classic essential, cerebellar, dystonic, and drug-induced tremors
Intention	Subtype of kinetic tremor amplified as the target is reached – presence of this type of tremor implies a disturbance of the cerebellum or its pathways
Rest	Occurs in a body part that is relaxed and completely supported against gravity – most commonly caused by Parkinsonism, but may also occur in severe essential tremor

Adapted from table from Ref. [22]

Differential Diagnosis

As above, the most common tremor is physiological, with essential tremor being second and Parkinson's tremor third. As Parkinson's was addressed in detail above, it will not be discussed in this section. Other considerations in those with tremor include cerebellar tremor, drug-induced tremor, dystonic tremor, and psychogenic tremor.

- **Essential Tremor (ET):** The most common pathological tremor is essential tremor. In - one-half of cases, it is transmitted in an autosomal dominant fashion, and it affects 0.4–6 % of the population. Careful history reveals that patients with essential tremor have it in early adulthood (or sooner), but most patients do not seek help for it until 70 years of age because of its progressive nature. Despite being sometimes called "benign essential tremor," essential

Table 5 Medications used for essential tremor

Class	Medications that can be used
Beta Blockers	Propranolol, atenolol, sotalol, nadolol, metoprolol
Anticonvulsants	Primidone, gabapentin, topiramate
Benzodiazepines	Alprazolam, clonazepam
Botulinum toxin type A	

tremor often causes severe social embarrassment, and up to 25 % of those afflicted retire early or modify their career path. Essential tremor is an action tremor, usually postural, but kinetic and even sporadic rest tremors have also been described. It is most obvious in the wrists and hands when patients hold their arms in front of themselves (resisting gravity); however, essential tremor can also affect the head, lower extremities, and voice. It is generally bilateral, is present with a variety of tasks, and interferes with activities of daily living. In a series of 200 Italian patients referred to a neurologist for evaluation of tremor, 15 % had uncommon clinical features that included postural, action, rest, orthostatic, and writing tremors, and 10 % had tongue or facial dyskinesia [23]. Diagnostic criteria for ET have not been universally accepted. Persons with essential tremor typically have no other neurological findings; therefore, it is often considered a diagnosis of exclusion. If the tremor responds to a therapeutic trial of alcohol consumption (two drinks per day), the diagnosis of essential tremor is assured [22].

If essential tremor is suspected, it is appropriate to begin pharmacological treatment. Many treatments have shown efficacy and are listed in Table 5. In addition to pharmacology, alcohol has been used for diagnostic and self-treatment purposes as ET will usually improve with alcohol intake. However, because of concerns for dependence and abuse, it should not generally be recommended for treatment purposes.

- **Beta blockers:** Of the beta blockers listed in Table 3, propranolol has been most proven to be effective in treating limb tremor and probably helps with head tremor as well. The effective dosage can be between 60 and 320 mg/day. Side effects include lightheadedness, fatigue, impotence, and bradycardia. The other beta blockers listed in the table have been shown to probably be effective for tremor, but their efficacy has not been established as much as propranolol [24, 25].
- **Anticonvulsants:** Primidone at doses up to 750 mg/day is effective in reducing tremor associated with ET. It should be started at much lower dosage (around 25 mg nightly) and titrated slowly to effectiveness. Side effects include sedation, drowsiness, fatigue, depression, nausea, vomiting, malaise, dizziness, confusion, vertigo, and acute toxic reaction. These are usually more severe at initiation of treatment. The other anticonvulsants listed may be effective but are not as commonly used [24, 25]. Gabapentin usually has fewer side effects than primidone, but topiramate often will have high rates of adverse effects.
- **Benzodiazepines:** Clinical trials have shown that alprazolam reduces tremor when compared to placebo. Mean effective dose for alprazolam was 0.75 mg/day [26]. Data regarding clonazepam is more conflicting, and it may reduce tremor if used.
- **Botulinum Toxin type A:** Botulinum Toxin has some effectiveness in limb tremor and may also reduce head tremor and voice tremor [24].

In those who do not respond well to pharmacological therapy or disease progresses, deep brain stimulation and thalamotomy are options which can be considered and are efficacious [24].

- **Enhanced Physiological Tremor:** A physiological tremor is present in all persons. It is a low-amplitude, high-frequency tremor at rest and during action that is not reported as symptomatic. This tremor can be enhanced by anxiety, stress, and certain medications and metabolic conditions. Patients with a tremor that comes and goes with anxiety, medication use, caffeine intake, or fatigue do not need further testing [22]. Treatment would be to discontinue the exacerbating factor.

Table 6 Medications and substances that may exacerbate tremor

Amiodarone	Hypoglycemic agents
Amphetamines	Lithium
Atorvastatin (Lipitor)	Metoclopramide (Reglan)
Beta-adrenergic agonists (e.g. albuterol)	Methylphenidate (Ritalin)
Caffeine	Terbutaline
Carbamazepine (Tegretol)	Theophylline
Corticosteroids	Thyroid hormones
Cyclosporine (Sandimmune)	Tricyclic antidepressants
Epinephrine	Valproic acid (Depakene)
Fluoxetine (Prozac)	Verapamil
Haloperidol	

From Refs. [22, 24, 25]

- **Drug- and Metabolic-Induced Tremors:** Many medications can cause or exacerbate tremor. Patients with new-onset tremor should have a comprehensive medication review with specific attention to medications started prior to the onset of tremor. Medications prone to inducing or activating tremor are listed in Table 6.

When medication review reveals a possible culprit, trial off of the medication should be attempted.

Metabolic causes of tremor are varied. Initial workup of tremor may include blood testing for hepatic encephalopathy, hypocalcemia, hypoglycemia, hyponatremia, hypomagnesemia, hyperparathyroidism, hyperthyroidism,, and vitamin B12 deficiency [22].

- **Cerebellar Tremor:** The classic cerebellar tremor presents as a disabling, low-frequency, slow intention or postural tremor and is typically caused by multiple sclerosis with cerebellar plaques, stroke, or brainstem tumors. Other neurological signs include dysmetria (overshoot on finger-to-nose testing), dyssynergia (abnormal heel-to-shin testing and/or ataxia), and hypotonia. Presence of these signs should prompt urgent head imaging with CT or MRI [22].
- **Psychogenic Tremor:** Differentiation of organic from psychogenic tremor can be difficult. Features consistent with psychogenic tremor are abrupt onset, spontaneous remission, changing tremor characteristics (can be resting, postural, and action), and extinction with distraction. It usually has a relatively constant frequency. Often, there is an associated stressful life event. Based on clinical experience, the prevalence of psychogenic tremor is thought to be high, but there are no precise estimates [22]. Electrophysiological testing can help with determining the frequency and disappearance with distraction. This can be a challenging diagnosis to make as patients will oftentimes refute it believing that there is another cause of their symptoms [27]. There are no universally accepted treatments for psychogenic tremor, though evidence suggests that psychotherapy, cognitive behavioral therapy, and antidepressant medications may help [28, 29].
- **Dystonic Tremor:** Dystonic tremor is a rare tremor found in 0.03 % of the population. It typically occurs in patients younger than 50 years. The tremor is usually irregular and jerky, and certain hand or arm positions will extinguish the tremor. Other signs of dystonia (e.g., abnormal flexion of the wrists) are usually present [22].

Family/Community Issues

IPD and ET can be very difficult diagnoses to deal with for both patients and their families. As a result, it may be necessary to refer patients to counseling who are feeling depressed. Family

counseling may be considered as well. It is also important for family physicians simply to understand the difficulty that they might be having and show empathy in their interactions.

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Family Medicine
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Disorders of the Peripheral Nervous System

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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 2–8 % 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. 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

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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

(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 have 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]. Conversely antiviral drugs alone have not been shown to benefit recovery [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, providers may need to provide psychological support to patients with this disfiguring condition [4, 5].

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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 Association for the Study of Pain [8]. Some authorities further classify the condition as classic (idiopathic) and symptomatic (associated with a structural abnormality) [9]. 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 symptomatic trigeminal neuralgia, though there is significant overlap with the classic form [10]. 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. 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 when the diagnosis is in question 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, anti-inflammatory medications and 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 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

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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 to 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. 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.

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 may be helpful, but surgical resection is often necessary.

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). Classic and disputed account 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. 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 [19].

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 [20]. 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 rapidly progressive pain of neck and shoulder followed

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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 [21].

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 [22].

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 varicella-zoster vaccine is available for persons 50 years of age and older and has been shown to reduce the incidence of herpes zoster by 51 % and incidence of postherpetic neuralgia by 66 %. 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 [23, 35].

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

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mononeuritis or mononeuritis 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 [24].

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 [24].

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 [24]. 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.

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 [27]. 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, 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 [28, 29]. Supportive care with invasive ventilation may be necessary. Intensive rehabilitation produces greater functional improvement and reduces disability in the later stages of recovery [27].

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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 1.2–7.7 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. Patients often spontaneously improve making clinical treatment trials difficult to interpret. IVIG and corticosteroids are considered first-line treatment. Small studies have shown some benefit of other immunomodulating agents [30].

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, amitriptyline, gabapentin, valproate, and topical capsaicin 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 [31].

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 [32]. 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 [25]. Risk factors for development of chemotherapy-induced peripheral neuropathy are baseline neuropathy, smoking, abnormal creatinine clearance, and specific sensory changes during chemotherapy [25]. 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 [26].

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. 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.

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 [33].

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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 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 [33].

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. 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. Patients with cobalamin malabsorption may be treated with oral supplements of 1000 mg daily as they will be able to absorb free cobalamin [33].

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 [33].

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 [33].

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.

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The genetics and pathophysiology of numerous hereditary neuropathies have been elucidated; however, just two types of hereditary motor and sensory neuropathies (HMSN I, 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 [34].

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 [35]. Gabapentin and pregabalin have the best evidence for treatment of painful diabetic neuropathy, postherpetic neuralgia, and central neuropathic pain [36]. Gabapentin and carbamazepine also show efficacy in treatment of pain associated with Guillain-Barre syndrome [37]. 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 [38].

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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 non-viral 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. The most common causes of fungal meningitis are *Cryptococcus neoformans* and *Cryptococcus gattii* [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 three 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 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 sensitivity and specificity for neck stiffness for meningitis are 30 % and 68 %, for Kernig's sign are 5 % and 95 %, and for Brudzinski's sign are 5 % and 95 %, respectively. 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.

Course and Prognosis

Without treatment, mortality of patients with bacterial meningitis approaches 100 %. However, even with treatment, the mortality rate for children is 3 % and for adults is 21 %. Hearing loss is seen in 14 % of adult patients and hemiparesis in 7 % of adult patients. Stroke is seen in 3 % of children [4, 5].

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 [6].

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 [7].

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 [5].

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 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

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]

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 including memory impairment, personality and behavioral change, dysphagia, and seizures [8–10].

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.

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 [11–13].

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 [14].

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 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) [15, 16].

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 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

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]

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 [17].

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) [18].

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 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 [19].

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) [20]. 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

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]

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.

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 [21].

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 [22].

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 [23].

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) [24, 25].

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 [26].

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.

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 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 [24].

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]
MS-typical regions of the CNS include periventricular, juxtacortical, infratentorial, or spinal cord

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 [25].

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Family Medicine
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The Red Eye

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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 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.

Conjunctivitis, whether infectious or noninfectious, is the most common cause of red eye presenting to the primary care setting. 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 [2, 3]. It is estimated that 70 % of all patients with acute conjunctivitis present to primary care and urgent care centers [4]. 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 [5].

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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
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
Herpes keratitis	Predominately 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	No
Acute glaucoma	Narrowing of the ant. chamber	Severe throbbing	Watery	Decreased	Partially dilated, nonreactive	Swelling	Elevated	Yes

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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	1 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 hours and qhs × 7–10 days * 1–2 drops every 2–3 h × 7–10 days	>2 months: * 0.5 in. ribbon every 3–4 hours and qhs × 7–10 days * 1–2 drops every 2–3 h × 7–10 days	Not first line due to potential sulfa allergy
Gentamicin (Garamycin)	0.3 % ointment 0.3 % solution	* 0.5 in. ribbon bid-tid * 1–2 drops every 4 h	>1 month: * 0.5 in. ribbon bid-tid * 1–2 drops every 4 h	May cause ocular burning
Tobramycin (Tobrex)	0.3 % solution	1–2 drops every 4 h	>2 months: 1–2 drops every 4 h	May cause ocular burning
Ciprofloxacin (Ciloxan)	0.3 % solution	1–2 drops every 2 h while awake and then every 4 h × 5 days	>1 year: 1–2 drops every 2 h while awake and then every 4 h × 5 days	Reserved for severe infections or contact lens wearers
Levofloxacin (Iquix, Quixin)	0.5 % solution	1–2 drops every 2 h while awake × 2 days and then every 4 h while awake × 5 days	>1 year: 1–2 drops every 2 h while awake × 2 days and then every 4 h while awake × 5 days	Reserved for severe infections or contact lens wearers
Ofloxacin (Ocuflox)	0.3 % solution	1–2 drops every 2–4 h × 2 days and then 1–2 drops qid × 5 days	>1 year: 1–2 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	1 drop every 2 h up to 8×/day × 1 day and then 1 drop bid-qid × 6 days	>1 year: 1 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	1 drop tid × 7 days	>1 year: 1 drop tid × 7 days	Reserved for severe infections or contact lens wearers

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

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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.

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.

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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 polio-like 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].

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 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 [5].

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.

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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 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.

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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]. 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 to treat the infection. Topical antibiotics may suppress the ocular symptoms but does 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 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.

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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.

Other Causes of Red Eyes

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 [24]. 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.

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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 [5]. Topical nonsteroidal anti-inflammatory drugs (NSAIDs) are not indicated and have been shown to have no significant benefit versus placebo [25]. 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 with an underlying systemic disorder, such as rheumatoid arthritis, Wegener's granulomatosis, and systemic lupus erythematosus, in up to 50 % of patients [26]. 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 [24]. If an underlying systemic disease is suspected or known, referral to rheumatology may be indicated.

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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 [27, 28]. Ten to thirty percent of patients with juvenile idiopathic arthritis develop chronic anterior uveitis, and it remains a cause of blindness in childhood [29]. 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 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 [30]. 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

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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 [31].

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 [32]. 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 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.

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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 [33]. 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.

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

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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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Contents

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According to a comprehensive survey of eye injuries in the United States published in 2005, 51 % of eye injuries are seen in the emergency room, while 47 % are treated by private practice physicians and in outpatient facilities [1]. Many of these patients will be seen by family physicians; the purpose of this chapter is to assist in correctly diagnosing and managing eye injuries.

In the United States, more than 40,000 eye injuries and 27 % of all pediatric ocular trauma hospital admissions were sports related [2, 3]. In Norwegian and Scottish studies, high percentages of eye injuries were caused by a ball, primarily soccer, and racquet sports [3]. Ninety percent of sports-related eye injuries are preventable with proper protective eyewear [4].

The chapter is divided into red eye, trauma, and burns. Each section covers the history and physical, treatment, and management for the diagnosis.

General Eye Exam

The eye is examined beginning with function, followed by structure, from the outermost to the innermost structures. Screen for vision loss using a Snellen eye chart at 20 ft (or near vision card, if necessary); record vision for each eye. If the patient is unable to use the eye chart, note presence or absence of light perception, hand movements, and ability to count fingers. Then inspect the lids and orbits. If there is significant swelling, palpate to determine the degree of edema or orbit involvement. Next, inspect the sclera and conjunctiva.

If there is a foreign body sensation, evert the upper lids to explore for foreign body. Topical anesthetic may be used. Use a cotton-tipped applicator to remove any foreign bodies from the internal surface of the upper lid. If cotton-tipped applicator is not successful, a sterile needle or eye spud may be used to flick out the foreign body. If there is a penetrating injury, do not attempt to remove a foreign body to avoid extrusion of eye contents.

Using direct ophthalmoscope, inspect the cornea for infiltrate or ulcer. Inspect the anterior chamber for hypopyon (pus) or hyphema (blood). Look for evidence of a penetrating eye injury. Assess the pupil to see if it is irregular in contour, dilated, or fixed. Examine for extrusion of ocular contents. These problems should be referred to ophthalmology on an urgent, same-day basis.

Use your office eye tray to procure the necessary items for fluorescein staining and inspection. The eye tray should include:

- Fluorescein stain strips
- Dropper bottle of sterile saline
- Cobalt blue light or black light
- Ophthalmic antibiotic ointment: erythromycin 0.5 % ointment
- Topical anesthetic: tetracaine hydrochloride 0.5 %, 1 % or proparacaine hydrochloride 0.5 %
- Topical mydriatic to dilate the pupil: phenylephrine 2.5 %,
- Topical cycloplegic, if needed for ciliary spasm: cyclopentolate 1 % (Cyclogyl) or homotropine 5 %
- Combined topical cycloplegic/mydriatic: tropicamide 0.5 %, 1 %
- Pocket-size Snellen chart
- Loupes for examiner to provide magnification

Moisten the strip with a drop of saline or topical anesthetic, pull down the lower lid, and gently touch the strip to the bulbar conjunctiva. Ask the patient to blink and the stain will be distributed over the cornea and conjunctiva. Inspect with magnification for patterns of injury.

Red Eye

The top causes of red eye are (1) conjunctivitis, (2) subconjunctival hemorrhage, and (3) corneal abrasions. Vision is the vital sign of the eye, so all patients should be screened for visual acuity with a hand-held Snellen chart or eye chart. For discussion of conjunctivitis, see chapter "► The Red Eye".

Subconjunctival Hemorrhage

Subconjunctival hemorrhage is painless and may occur spontaneously, after rubbing the eye, or in the setting of Valsalva maneuver, such as persistent coughing or a woman straining in labor. Direct visual inspection of the eye reveals the diagnosis. It is harmless and will resolve spontaneously without treatment within 2 weeks. While subconjunctival hemorrhage is usually benign, if extensive and mechanism of injury is traumatic, consider occult globe rupture [4].

A more concerning cause of red eye is corneal abrasion which usually causes eye irritation and may be accompanied by the presence of a foreign body.

Corneal Abrasions and Foreign Bodies

Corneal abrasions account for approximately 8 % of ocular cases in the primary care setting [5]. Correct diagnosis and early treatment is important. For although these injuries heal quickly, they have the potential to cause scarring and subsequent loss in visual acuity.

History and Physical Exam

Patient may present with eye pain and tearing, sensitivity to light, and foreign body sensation. There may be a history of eye rubbing. Common sources of injury include applying mascara, working with wood or metal, working in a dusty environment, and wearing contact lens. Mechanism of injury is important for the differential diagnosis.

Linear or blocky defects may be due to trauma. Punctate lesions may be associated with infection or ulceration in contact lens wearers. A branching pattern is worrisome for herpes simplex keratitis, which requires urgent, same-day referral to ophthalmology. A scratch pattern of vertical lines suggests foreign body under the upper lid. A pattern of diffuse generalized uptake is consistent with conjunctivitis, viral or bacterial. Figure 1

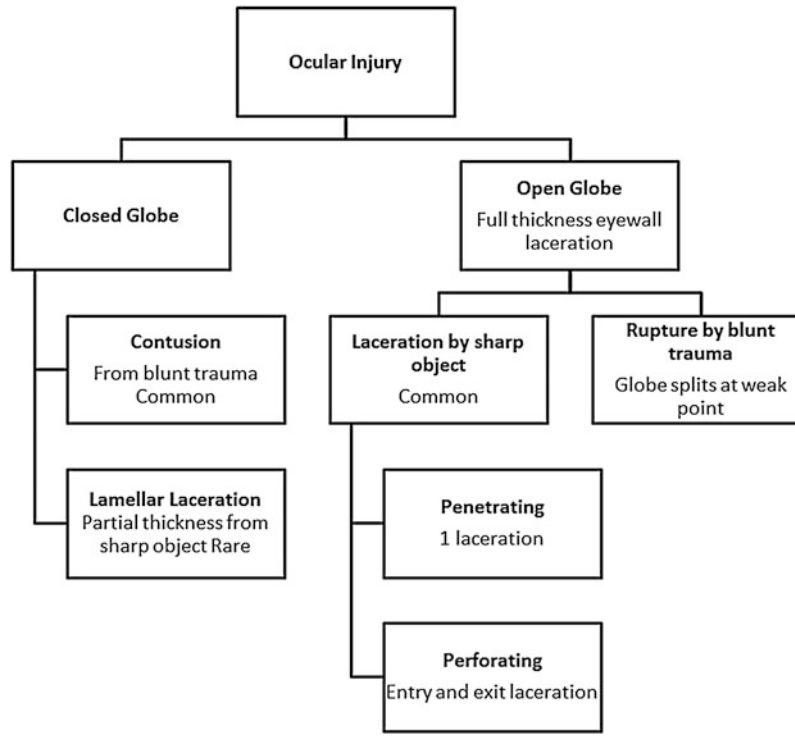

Fig. 1 Evaluation and management of corneal abrasions (Modified from Wipperman [7])

Table 1 Topical ophthalmologic medications for treatment of corneal abrasion

Medication	Dosage	Cost estimate[a] Generic cost (brand cost)
Home treatment		
Topical antibiotics		
Erythromycin 0.5 % ointment	0.5-in. ribbon, four times per day for 3–5 days	$17.86 (NA) for 3.5-g tube
Polymyxin B/trimethoprim (Polytrim) solution	1 drop, four times per day for 3–5 days	$4 ($57.48) for 10 ml eyedropper
Sulfacetamide 10 % (Bleph-10) solution	1–2 drops, four times per day for 3–5 days	$4 ($98.35) for 1 15 ml eyedropper
Antipseudomonal antibiotics		
Ciprofloxacin 0.3 % (Ciloxan) ointment	0.5-in. ribbon, four times per day for 3–5 days	NA ($135.05) for 3.5-g tube
Ciprofloxacin 0.3 % (Ciloxan) solution	1 drop, four times per day for 3–5 days	$10.97 ($100.37) for 5 ml eye dropper
Gentamicin 0.3 % ointment	0.5-in. ribbon, two to three times per day for 3–5 days	$13.56 (NA) for 3.5-g tube
Gentamicin 0.3 % solution	1 drop, four times per day for 3–5 days	$4 (NA) for 5 ml eye dropper
Ofloxacin 0.3 % (Ocuflox) solution	1 drop, four times per day for 3–5 days	$5 ($88.27) for 5 ml eye dropper
Topical NSAIDs		
Diclofenac 0.1 % (Voltaren)	1 drop, four times per day for 2–3 days	$15.64 ($80.20) for 5 ml eye dropper
Ketorolac 0.4 % (Acular LS)	1 drop, four times per day for 2–3 days	$15.00 ($191.09) for 5 ml eye dropper
Office treatment		
Topical cycloplegics[b]		
Cyclopentolate 1 % (Cyclogyl)	1 drop, may repeat in 5 min if needed	$5 ($24) for 2 ml eye dropper
Homatropine 5 %	1 drop, may repeat in 5 min if needed	

NA not available
[a]Estimated price of treatment based on information obtained at www.goodrx.com
[b]All Pregnancy Class C

provides a flowchart to assist in the diagnosis and treatment of corneal abrasions.

Treatment and Management

If a corneal abrasion is identified, treatment is targeted to prevent pain and infection. Table 1 provides common medications that can be prescribed for corneal abrasions and foreign bodies. The corneal epithelium grows rapidly and usually uncomplicated abrasions heal in 24–48 h. An abrasion of 4 mm or less with normal vision may not require follow-up as long as symptoms resolve within 24 h. For patients with diminished vision, contact lens wearers, and abrasions greater than 4 mm, arrange for follow-up in 24 h. A review of the literature has reported that patching v. nonpatching plays no significant role in the patient's prognosis [6].

Eyelid Lacerations

History

Patients with eyelid lacerations present with periorbital pain and tearing. Determine the extent of the injury: a partial- or full-thickness defect of the eyelid involves the skin and the subcutaneous

tissue. Superficial lacerations or abrasions may mask a deep laceration or injury to the lacrimal drainage system (e.g., puncta, canaliculi, common canaliculus, lacrimal sac), the orbit, the globe, or the cranial vault.

In accidents or altercations, details of the history will help determine the mechanism of injury and the likelihood of a foreign body [8].

Physical Exam

When examining superficial eyelid lacerations, first rule out a globe injury. Full-thickness lacerations, especially those involving the lid margin, warrant an immediate referral to an ophthalmologist. Do not forcibly open a lid swollen shut by edema or hematoma, as this could express eye contents through a previously undiscovered laceration. Refer to ophthalmology for more complete examination [4].

Complete an ocular examination, including bilateral dilated evaluation of the fundus. Ensure there are no injuries to the globe and optic nerve before attempting eyelid repair. Evert the lid, and use toothed forceps or cotton-tipped applicators to gently pull open one edge of the wound to determine the depth of penetration [4].

Treatment and Management

For superficial eyelid lacerations, use sterile superficial skin closures if only skin is involved.

Globe Injuries

Injury types are classified in a standardized manner using the Birmingham Eye Trauma Terminology criteria [9]. Figure 2 provides a modified BETTS for ocular trauma.

Closed-globe injuries are most commonly caused by blunt trauma. Blunt trauma commonly occurs in sports [3, 4]. The eye wall is not completely penetrated, whereas in open-globe injuries, there is a full-thickness wound.

Closed-Globe Injuries

Closed-globe injuries from blunt trauma most commonly cause contusions. However, when partial thickness wounds of the eye wall (lamellar lacerations) occur, these are usually caused by a sharp object.

The size of the object causing blunt force can determine the type of injury. Objects smaller than the orbital opening (e.g., golf, racquet, and squash balls) cause rapid interior-posterior compression of the globe, dilation of the middle of the globe, and extreme force on internal ocular structures. The lens-iris diaphragm absorbs most of the force. When the highly vascular iris bleeds, red blood cell sediments create a fluid level in the anterior chamber called "hyphema." Objects larger than the orbital opening allow "a pressure release valve," protecting eye structures by fracturing the thin bones at the floor and medial wall of the orbit ("blow out fractures of the orbit") [10].

Hyphema

History and Physical Exam

Patients with hyphema complain of decreased visual acuity and pain. Blood may be grossly visible, appearing black or red [5]. If the pupil in the traumatized eye does not constrict with light exposure, traumatic ocular neuropathy should be suspected. Understanding the mechanism of injury is an important step in determining the extent of damage. Patients' medications should also be examined for anticoagulants or a history of sickle cell disease and coagulopathies [5].

Treatment and Management

The severity of hyphema dictates the management. Hyphemas are graded based on the amount of the anterior chamber which is filled with blood (from Grade 0-microhyphema, which is only visible by slit lamp to Grade IV, which is completely

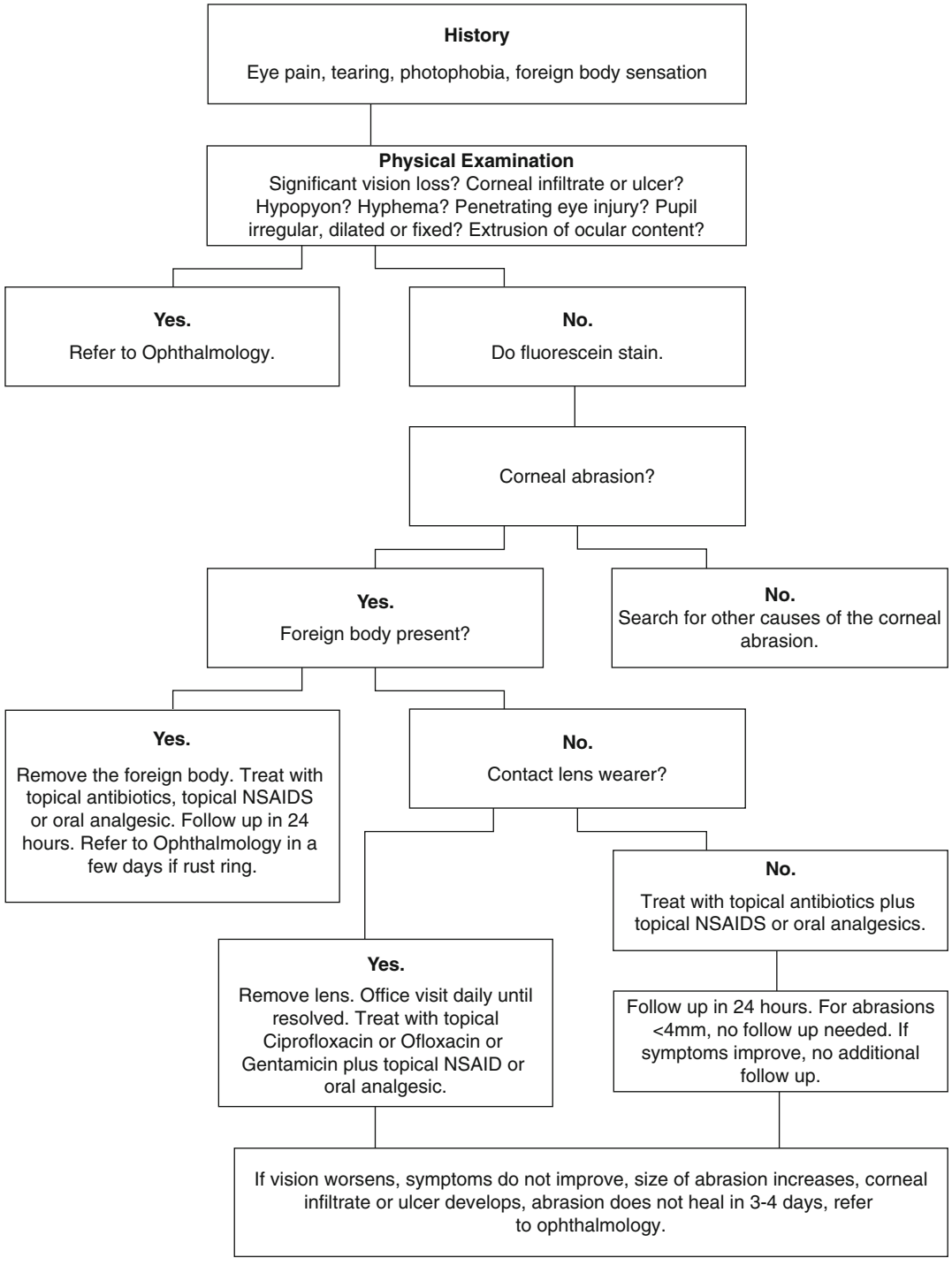

Fig. 2 Modified Birmingham Eye Trauma Terminology system classification for ocular trauma [9]

filled with clotted blood). Use of an eye shield, limited activity, and head elevation are usual for uncomplicated hyphema. Severe hyphemas require a referral to ophthalmology. In a recent review, the benefits of treating hyphemas with corticosteroids or antifibrinolytics were inconclusive [6].

Traumatic Retrobulbar Hemorrhage

History and Physical Exam

Arteries behind the globe can shear with blunt trauma. The bleeding causes the globe to press forward, causing increased intraocular pressure due to resistance from anterior structures. Continued pressure results in optic nerve damage and decreased blood flow in the central retinal artery.

Clinical presentation includes pain, decreased vision, and inability to open the eyelid due to severe swelling. Patient may have massive subconjunctival hemorrhage with no posterior border. Other signs are proptosis, hard eyelids, and a tense orbit that cannot be moved posteriorly on palpation. Extraocular movements are limited; pupillary reaction may be normal, or as damage to the optic nerve progresses, an afferent pupillary defect develops [3, 8].

Treatment and Management

Assessment includes fundoscopic exam and measurement of intraocular pressure. Refer to ophthalmology for medication to decrease intraocular pressure and/or surgery [3, 8].

Blowout Fractures

History and Physical Exam

Double vision with a vertical gaze and pain with vertical eye movement is the classic clinical presentation of an orbital floor blowout fracture. Pain with horizontal eye movement suggests orbital fracture at the medial wall [8]. The sudden increase in intraocular pressure which leads to orbital fracture can damage the trabecular meshwork and cause glaucoma and cataract formation [10]. One-third of these injuries occur during sport participation [11].

Swelling of the eyelids after sneezing or blowing the nose suggests communication between the sinus and the orbit. Other symptoms are sunken eye (enophthalmos which may be obscured by edema), decreased extraocular movements, and tenderness at the rim of the orbit [3, 8]. There may be "orbital emphysema" due to air entering the orbit. Cheek numbness indicates injury to the infraorbital nerve [8].

"Trapdoor" fractures are detected by significant extraocular muscle restriction (usually vertical) on exam. Pediatric patients may not have external swelling or lacerations due to the flexibility of their bones. When children have diplopia, they may close one eye rather than report double vision. In pediatric head trauma, symptoms of nausea, vomiting, bradycardia, and syncope may represent an oculocardiac reflex, rather than concussion [8].

Treatment and Management

Apply cold compresses to reduce edema and advise patient to avoid blowing nose or sneezing. Use an ice pack for 20 min per hour for the first 24–48 h and incline the head at 30° when at rest. If a communication between the sinus and the orbit is suspected, use nasal decongestants (e.g. oxymetazoline nasal spray b.i.d. for 3 days) and antibiotics. Antibiotics are also appropriate for patients who are immunocompromised, and those who have chronic sinusitis or diabetes. Antibiotic choices include cephalexin 250–500 mg p.o. q.i.d., erythromycin 250–500 p.o. q.i.d., or doxycycline 100 mg p.o. b.i.d. for 7 days.

For severe swelling which interferes with examination, consider oral corticosteroids. Concomitant oral antibiotics may be prudent to prevent infection. Consider consultation of neurosurgery. If fracture of the frontal sinus, midface, or mandibles is involved, consider

consultation of otolaryngology or oral maxillofacial surgery [8].

Particularly in pediatric patients, CT of the orbits with fine cuts and attention to the coronal views is critical to detect rectus muscle incarceration or "missing" inferior rectus [8].

Open-Globe Injuries

Open-globe injuries are full-thickness wounds of the eye wall, most commonly caused by trauma from sharp objects. Most open-globe injuries are caused by laceration from a sharp object. Open-globe lacerations are determined to be penetrating (single laceration) or perforating (two lacerations that enter and exit the eye wall).

Injuries caused by sharp objects are more common in males than females 3:1 [9]. Mechanism of injury is often due to high velocity splinters of metal or wood, which can occur during hammering (metal on metal or metal on stone), woodworking, or use of power tools. In the pediatric population, mechanisms of injury include compressed air-powered guns (paint ball and BB guns), fireworks, darts, and bungee cords [2]. Males also predominate in pediatric eye injuries.

History and Physical Exam

Patients commonly complain of a foreign body sensation, pain, and decreased visual acuity.

Globe Rupture

History and Physical Exam

Globe rupture occurs when severe blunt trauma causes the globe to split at the weakest point. Twenty percent are missed on initial presentation [12]. Findings associated with ruptured globe include irregular or oval pupil, hyphema, irregular-shaped iris, laceration with dehiscence of tissue, or leakage of fluid.

Treatment and Management of Open-Globe Injury and Globe Rupture

If open-globe injury or globe rupture is suspected, do not instill topical antibiotics or apply pressure to the eye. Patient should avoid Valsalva maneuver to prevent extrusion of ocular contents. Patients who are nauseated or vomiting should be given antiemetics. To protect against endophthalmitis, administer antibiotics with coverage for staph and strep. Antibiotic options include the oral fluoroquinolones levofloxacin (500 mg every 12 h) or moxifloxacin (400 mg every 12 h) due to excellent vitreous penetration. IV antibiotics vancomycin (1 g every 12 h) or ceftazidime (1 g every 8 h) are good alternatives [13].

After placing a protective eye shield, refer to ophthalmology immediately. CT is used to rule out intraocular foreign body. Surgical repair is recommended within 24 h.

Posterior Segment Injuries

Any of the previous described traumatic mechanisms of injury can result in posterior segment injuries. Posterior segment injuries include vitreous hemorrhage, retinal detachment, and damage to the optic nerve.

Retinal Detachment

History and Physical Exam

The typical presentation of retinal detachment is acute unilateral vision loss with floaters and flashing lights. The neurosensory layer of the retina pulls off the underlying pigment epithelium. This is usually caused by detachment of the vitreous which pulls on the retina and may cause a retinal tear. Rapid diagnosis is helpful since early treatment will minimize permanent vision loss.

Dilated funduscopic exam usually reveals retinal detachment. However, cataracts, corneal scars, or vitreous hemorrhage may obscure the retina. In that case, ultrasound is necessary for diagnosis.

Treatment and Management

Same-day referral to ophthalmology will allow treatment using laser photocoagulation to seal retinal tear, if present, and reattach the retina to the underlying epithelium. Key to prognosis is whether the macula is involved. Ophthalmology follow-up is required since patients are at a high risk for recurrent retinal detachment or detachment of the retina in the other eye [13].

Optic Nerve Injury

History and Physical Exam

Optic nerve injury can be direct (compression from bone, foreign body, edema) or indirect (shearing injury from blunt trauma to the head) [3]. Optic nerve injury is suggested by loss of afferent pupillary reflex and decreased ability to see red in the central field of vision. In the swinging flashlight test, the affected pupil will paradoxically dilate with direct illumination. This is because the light has been removed from the functioning optic nerve in the healthy eye causing dilation of both pupils since the injured optic nerve does not sense the incoming light (Marcus Gunn pupil).

Evaluation should also include dilated eye exam, visual fields, visual acuity, and color vision testing. CT scan of the orbits and head may demonstrate compressive injuries not seen on direct ophthalmoscopy.

Treatment or Management

If optic nerve injury is suspected, refer for same-day ophthalmology consultation and high-dose corticosteroids. Optic nerve injuries may result in permanent visual loss.

Shaken Baby Syndrome

Shaken baby syndrome is a triad of retinal hemorrhage, encephalopathy, and subdural hematomas. The pattern of retinal hemorrhage in shaken baby syndrome is widespread distribution, occurring at multiple depths, and too numerous to count. Any retinal hemorrhage in the setting of unexplained trauma should raise suspicion of inflicted injury [2].

Burns

Chemical Burns

Chemical burns are caused by an number of caustic agents including alkali (e.g., lye, cements, plasters, airbag powder, bleach, ammonia), acids (e.g., battery acid, pool cleaner, vinegar), solvents, detergents, and irritants (e.g., mace). The most common alkali burns involve ammonia, lime, and sodium hydroxide. Alkali burns are twice as common as acid burns and more severe, due to penetration of tissue and precipitation of glycosaminoglycans [10]. Chemical burns are a common cause of ocular trauma in males ages 16–45 as a result of accidents (work and home) or criminal assault [5]. The most common acid burns are hydrochloric acid and sulfuric acid. In the case of a chemical burn, treatment should begin immediately, even before vision testing, unless an open globe is suspected.

Emergency treatment includes copious saline irrigation for at least 20 min. One to 2 l of saline or lactated ringers should be run over the involved eye(s) using the Morgan lens irrigation apparatus. For alkali burns, tap water may be more efficacious in inhibiting elevated intracameral pH than normal saline. Never use acidic solutions to neutralize alkalis or vice versa as acid-base reactions themselves can generate harmful substrates. Irrigation is continued until neutral pH is achieved (i.e., 7–7.4) [8].

History and Physical Exam

With a chemical burn, it is critical to determine the time of exposure, the type of material, the time between exposure and irrigation, the duration and type of irrigation, and whether any eye protection was involved [5].

Table 2 Modified Dua classification for ocular surface burns

Grade	Prognosis	Clinical findings	Conjunctival involvement
I	Very good	0 clock hours of limbal involvement	0 %
II	Good	<3 clock hours of limbal involvement	<30 %
III	Good	Between 3 and 6 clock hours of limbal involvement	30–50 %
IV	Good to guarded	Between 6 and 9 clock hours of limbal involvement	50–75 %
V	Guarded to poor	Between 9 and 12 clock hours of limbal involvement	75–100 %
VI	Very poor	Total limbus involved	Total conjunctival involvement

Modified from Dua et al. [14]

Following emergency treatment, perform a slit-lamp examination with fluorescein staining to identify any corneal or conjunctival ulceration. Eyelid eversion should be performed to identify and remove any foreign bodies. The Dua classification system is helpful when referring patients to ophthalmology [5, 14] (Table 2).

Treatment and Management

Prescribe a topical antibiotic ointment, oral pain medication, and Cycloplegic. If IOP is elevated, acetazolamide 250 mg p.o. q.i.d., acetazolamide 500 mg sequel p.o. b.i.d., or methazolamide 25–50 mg p.o. b.i.d. or t.i.d. may be given. Electrolytes, especially potassium, should be monitored in patients on these medications. Add a topical beta-blocker (e.g., timolol 0.5 % b.i.d.) if additional IOP control is required. Alpha-agonists may be avoided because of their vasoconstrictive properties.

Initially, follow-up is daily, then every few days until the corneal epithelial defect is healed. Topical steroids may be used to reduce inflammation. Monitor for corneal epithelial breakdown, stromal thinning, and infection [8].

Ultraviolet Burns

Radiation injuries, or UV burns, occur as a result of exposure to ultraviolet light in snow skiing, water skiing, and other water sports. For example, snow blindness results from prolonged exposure to UV-B rays reflected from snow.

History and Physical Exam

Patients with UV burns typically present with intense pain, photophobia, and often a delay in symptom onset [4].

A fine punctate staining with fluorescein is characteristic.

Treatment and Management

UV burns are generally treated with a systemic analgesic and topical antibiotic. If epithelial defect is present, refer to an ophthalmologist. Prognosis is excellent following treatment.

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Family Medicine
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Otitis Media and Externa

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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.

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]. 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, 5].

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 overdiagnosis 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, 8]. 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.

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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

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 [10–12]. Narcotic pain medications, antihistamines, and decongestants are associated with significant side effects that outweigh any potential analgesic benefit for AOM [10, 13]. Other pain relief options may include naturopathic remedies or osteopathic manipulation though randomized controlled trials that demonstrate effectiveness of these options are limited [14, 15].

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° Celsius in the last 48 h, or uncertain ability to follow-up [6]. 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]. 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]. 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, 18].

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 [19].

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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, 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 [27–30]. 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 [31]. Formula-fed infants may benefit from probiotics such as *Lactobacillus rhamnosus* GG and *Bifidobacterium lactis* Bb-12 [32]. However, exclusive breastfeeding may be more beneficial as a risk reduction strategy than probiotic-supplemented formula [3]. 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 is defined as inflammation of the external auditory canal. It may be classified as acute, lasting less than 6 weeks, or chronic, lasting more that 3 months. Most cases of acute otitis externa (AOE) are infectious, while most cases of chronic otitis externa (COE) are allergic or related to a dermatologic condition.

Epidemiology

AOE is a disease of the young, with 95 % of cases occurring at those aged 18 years or younger [33]. It tends to occur in the summer and in warmer, humid climates. Risk factors include repetitive ear trauma, water exposure, hearing aids, and underlying dermatologic conditions such as eczema or psoriasis.

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Pathophysiology

Trauma to the epithelial lining of the ear canal, lack of cerumen, and disturbance of the normal acidic environment can lead to bacterial or fungal infection causing an inflammatory response. Cerumen protects the ear canal by limiting exposure to moisture, creating a slightly acidic pH and inhibiting bacterial growth through lysozymal activity. Self-cleaning the ear canal, such as with cotton swabs, not only removes cerumen but traumatizes the ear canal, and is a common cause of AOE. Excessive water exposure, such as in swimmers ("swimmer's ear"), can cause maceration and breakdown of the epithelial lining.

Most (98 %) cases of AOE are bacterial [34]. *Pseudomonas aeruginosa* and *Staphylococcus spp.* are most often implicated, and AOE may be a polymicrobial infection. Fungal infection (otomycosis) is uncommon but may be seen after treatment of AOE with topical antibiotics.

Diagnosis

Patients with AOE present with the rapid onset of ear pain, itching, or fullness (Table 1) [35]. Some patients also experience hearing loss, due to obstruction of the ear canal, or jaw pain. On physical exam, tenderness of the pinna or tragus is the hallmark of AOE. Early in its course, the tenderness is often severe and disproportionate to physical exam findings. As AOE progresses, the ear canal may become diffusely edematous and erythematous, with otorrhea that obstructs the tympanic membrane. Regional lymphadenitis or cellulitis of the pinna and surrounding skin may occur.

AOE can lead to inflammation of the tympanic membrane, making distinction between AOE and AOM difficult. Furthermore, AOE and AOM may co-occur and should be treated as separate entities. Pneumatic otoscopy and tympanometry are useful to help differentiate the two. Mobility of the tympanic membrane with pneumatic otoscopy and a normal peaked curve (type A) on tympanometry help rule out a middle ear effusion. In addition, normal tympanometry is indicative of an intact tympanic membrane, which is useful when the tympanic membrane is obstructed by canal edema and debris.

Obtaining cultures for bacteria and fungi is not generally needed for AOE. However, cultures should be obtained in patients with recalcitrant or recurrent cases, frequent topical antibiotic use, or immunocompromised states.

Treatment

Successful management of AOE includes aural toilet, treatment of infection, pain control, and avoiding promoting factors. Removing debris and impacted cerumen will allow topical antibiotics to penetrate the ear more effectively and enhance healing. Additionally, it important to ensure that there are no retained foreign bodies, especially in children. Debris may be cleared using gentle suction or direct visualization with an otoscope and blotting with a cotton swab or ear speculum. Irrigation may be used if the tympanic membrane is intact, but should be avoided in patients who are immunocompromised or with diabetes mellitus as there is an increased risk of malignant otitis externa [36]. Placement of an ear wick facilitates drug delivery if there is significant canal edema.

Topical therapy is the mainstay of treatment for AOE (Table 2). Generally, antiseptic and antibiotic preparations have similar effectiveness, and there is little difference between antibiotic classes [37]. Therefore, treatment should be based on convenience, cost, and potential adverse effects. Acetic acid 2 %

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Table 2 Common topical preparations for acute otitis externa

Component	Brand name	Cost[a]	Dosage	Comments
Acetic Acid 2 % solution	VoSol	$	3–5 drops every 4–6 h	Avoid if TM perforated. May cause local irritation
Acetic acid 2 %/hydrocortisone 1 % solution	VoSol HC	$$$	3–5 drops every 4–6 h	As above
Neomycin/polymyxin B/hydrocortisone solution	Cortisporin	$	3–4 drops every 6–8 h	Avoid if TM perforated
Ciprofloxacin 0.2 % solution	Cetraxal otic	$$	3–4 drops every 12 h	Single-use containers
Ciprofloxacin 0.2 %/hydrocortisone 1 % suspension	Cipro HC	$$$	3–4 drops every 12 h	
Ciprofloxacin 0.3 %/dexamethasone 0.1 % suspension	Ciprodex	$$$	3–4 drops every 12 h	
Ofloxacin 0.3 % solution	Floxin otic	$	10 drops once daily	
Dexamethasone 0.1 % suspension	Maxidex	$$		

[a]Based on generic price if available. Cost information obtained from www.goodrx.com; $ = 0–50 USD, $$ = 50–100 USD, $$$ = >100 USD

(VoSol) is inexpensive and provides similar cure rates to topical antibiotics in mild cases of AOE. However, it may cause local irritation and, due to ototoxicity, should be avoided if the tympanic membrane is not intact.

Topical antibiotics include fluoroquinolone and aminoglycoside preparations, which are effective against *Pseudomonas* and *Staphylococcus spp*. Aminoglycoside preparations are usually inexpensive and well tolerated. However, they require frequent (four times daily) dosing and are ototoxic to the inner ear. Neomycin, which is a found in Cortisporin otic, is a frequent cause of contact dermatitis. Fluoroquinolones are dosed twice daily and are the treatment of choice if the tympanic membrane is not intact or cannot be visualized. However, most fluoroquinolone preparations are more costly. Many topical preparations are available in combination with a steroid, which hastens resolution of pain and itching [38]. Patients should be treated for 7 days. If symptoms are not resolved, drops may be continued until resolution and then continued for 2–3 more days. Systemic antibiotics are not needed in most cases of AOE. Topical antibiotics reach high concentrations in the ear canal and are effective even against resistant bacterial strains. Systemic antibiotics, usually a fluoroquinolone (ciprofloxacin 500 mg twice daily for 7–10 days), are indicated if there is surrounding cellulitis, if canal edema limits penetration of topical antibiotics, or if the patient is immunocompromised.

Patient education on administration of topical preparations is paramount to successful treatment. Drops should be applied with the patient lying on their side with the affected ear up. Application is more successful if another person administers the drops. Enough drops should be instilled until the entire canal is filled, gently pulling the pinna to and fro to eliminate air trapping. Patients should wait 3–5 min before sitting up.

Pain control is achieved with over-the-counter analgesics such as acetaminophen or nonsteroidal anti-inflammatory drugs. Severe cases may require opioid analgesics. Topical benzocaine should be avoided as continued use can mask progression of disease; it is also ototoxic and can cause a contact dermatitis.

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Monitoring

Most patients improve dramatically within 48–72 h and have minimal or no symptoms by 7 days. If there is no improvement within 48 h, or symptoms continue for more than 14 days, patients should be reevaluated. Common causes for treatment failure include inadequate drug delivery, canal obstruction, or misdiagnosis. Referral to an otolaryngologist is indicated if there is lack of expected improvement, inability to remove debris, or suspected malignant otitis externa.

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. Malignant otitis externa is a severe, life-threatening complication of AOE and occurs most often in diabetic adult patients [39]. Infection spreads from the skin of the ear canal to bone of the skull base (osteomyelitis), causing severe pain, canal erythema, edema, and otorrhea. Granulation tissue is often visualized on the floor of the ear canal. Patients may have fever and signs of systemic toxicity. Sedimentation rate is usually significantly elevated, and diagnosis is confirmed with imaging by computed tomography or magnetic resonance imaging. Treatment requires intravenous antibiotics that cover *Pseudomonas* and potentially surgical debridement.

Prevention

Patients with AOE should avoid water immersion for 7–10 days. Patients may place a petroleum jelly-coated cotton ball in the affected ear while bathing. Competitive swimmers may return to play after 2–3 days if pain is resolved and they use well-fitting earplugs. Hearing aids should be avoided until pain has subsided.

To prevent future episodes, moisture retention in the ear canal should be minimized. Acidifying drops, such as acetic acid 2 %, or a hair dryer on the lowest setting, can be used to dry out the ear canal after swimming. Well-fitting earplugs can also limit water exposure. Any trauma to the ear is best avoided, including frequent ear cleaning and poorly fitting hearing aids.

Chronic Otitis Externa

Chronic otitis externa is a common pathway for several disease states and should be considered in the differential diagnosis of AOE (Table 3). Chronic inflammation of the ear canal may be due to allergic contact dermatitis, dermatologic conditions such as psoriasis, or chronic bacterial or fungal infection. Patients usually have more itching than pain. Contact dermatitis causes a maculopapular rash with excoriations on the external ear. Patients with psoriasis and atopic dermatitis may have an eczematous, lichenified appearance to the ear canal and external ear. In seborrheic dermatitis, the ear canal often lacks cerumen and is erythematous with dry, flaky skin. COE may result from chronic otitis media with tympanic membrane perforation, as the drainage causes chronic irritation and infection. In otomycosis, fluffy, cotton-like debris may be seen in the canal, as well as with sprouting hyphae or black dots. Culture for bacteria and fungi is prudent if chronic infection is suspected.

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Table 3 Differential diagnosis of acute otitis externa

Carcinoma of the ear canal
Chronic suppurative otitis media
Contact dermatitis
Eczema or Psoriasis
Furunculosis
Herpes zoster oticus
Malignant otitis externa
Otomycosis
Seborrheic dermatitis

Treatment of COE depends on the cause. For most dermatologic conditions, a medium-to-high-potency topical steroid is effective. Clotrimazole 1 % solution or cream treats most fungal otitis externa. Patients with bacterial infection should be managed as for AOE.

Box 1: Diagnostic Criteria for Acute Otitis Externa

1. Rapid onset (generally within 48 h) in the past 3 weeks
2. Symptoms of ear canal inflammation that include:
   - Otalgia (often severe), itching, or fullness
   - *With or without* hearing loss or jaw pain
3. Signs of ear canal inflammation that include:
   - Tenderness of the tragus, pinna, or both
   - Diffuse ear canal edema, erythema, or both
   - *With or without* otorrhea, regional lymphadenitis, tympanic membrane erythema, or cellulitis of the pinna and adjacent skin

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Family Medicine
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Disorders of the Oral Cavity

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Healthy People 2020 lists oral health as one of its top nine health indicators [1]. Diseases of the oral cavity can have a significant impact on the overall health of the individual patient. The mouth can provide a window to the body. Disease in the mouth can cause systemic disease such as endocarditis, make chronic disease management such as diabetes more difficult, or provide clues to the timely diagnosis of systemic disease [2].

Caries

Dental caries or tooth decay is the most common infection or chronic disease affecting the mouth [3–5]. Half of US seniors perceive their dental health as poor or very poor, and less than 50 % of people age 2 years and older have had a regular dental check-up in the last 12 months [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 [2–4]. Dental caries develops through the complex interaction of oral microorganisms (*Streptococcus mutans* and lactobacilli), metabolizing dietary sugars into lactic acid creating an acidic environment [2, 4, 5]. 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 [3, 4]. 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 [3, 4]. Once again definitive treatment involves mechanical removal of the decay through either restoration or extraction by a dentist. Insufficient evidence exists in the literature to recommend antibiotic therapy, unless infection has spread to the surrounding soft tissue [3–5].

Dental exams should begin when 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 [3]. 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 [3]. Parents should introduce toothbrushing with a pea-size amount of low-fluoride toothpaste to children at 2 years of age. In children younger than 2 years, parental brushing without toothpaste is recommended. After the age of six, children can safely use regular fluoridated toothpaste. The use of mouth rinses and gels at home is not recommended for children younger than six years. Toothbrushing with fluoridated toothpaste twice a day after meals is recommended as an effective way to prevent tooth decay on exposed surfaces, and flossing

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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 [4]. 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. Additionally, dietary changes such as reducing the amount and frequency of foods with high sugar content may further decrease dental caries rates.

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's syndrome, Papillion–Lefevre syndrome, diabetes, xerostomia, medications, and smoking may further dispose a patient to periodontal disease [2–3, 5]. Some evidence also suggests that the presence of chronic periodontal disease may exacerbate the progression of certain diseases such as diabetes and cardiovascular disease [3, 5]. Periodontal disease can be divided into gingivitis and periodontitis.

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. Medications such as phenytoin, calcium channel blockers, and cyclosporine can also lead to increased inflammatory or noninflammatory gingival hyperplasia [4]. 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 toothbrushing, daily flossing, and use of warm saline or chlorhexidine gluconate 0.12 % rinses [3, 4]. Mouth rinses containing essential oils such as Listerine has been shown to be as effective as chlorhexidine but with less tooth staining [3, 4]. Antibiotics are not necessary unless patient presents with acute necrotizing ulcerative gingivitis also known as Vincent's disease or trench mouth [5]. 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 [5]. 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 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*

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gingivalis, and spirochetes [5]. 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 [3, 4]. Antibiotic regimes include doxycycline 100 mg daily, metronidazole 500 mg orally twice daily, or topical application of metronidazole, doxycycline, or minocycline [2–3, 4]. Periodontitis is a common and serious condition affecting approximately 20 % of all adults and is the leading cause of tooth loss [4]. Besides causing focal oral disease, multiple studies demonstrate an association between periodontitis and cardiovascular disease, worsening diabetes, and increased risk for preterm labor [2, 4]. However, no study has demonstrated whether treating or preventing periodontal disease leads to improved systemic disease outcomes [4].

Candidiasis

Candida species are normal inhabitants of the gastrointestinal tract and present as part of the normal oral flora in sixty percent of healthy adults [2, 4, 6]. Certain local and systemic factors may make certain individuals more susceptible to oral candidal infections. These include infection with 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 [2, 4, 6]. Oral candidiasis is common in infants, affecting 1–37 % of newborns [6]. 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, 4, 6]. 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. 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.

Stomatitis

Characterized by inflammation of the mucosal lining of the mouth, lesions are erythematous, are 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 [4, 6]. 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 [6]. Treatment focus is on providing topical relief (see Table 1). Since disease course is generally self-limited, when an ulcer persists beyond

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Table 1 Topical agents for symptom relief of aphthous ulcers

Two percent viscous lidocaine (swish and spit)
Topical steroid (Kenalog) in Orabase three to four times daily
Miracle mouthwash: various combinations in equal parts (swish and spit several times daily)
Maalox or Mylanta, diphenhydramine, 2 % viscous lidocaine
Maalox or Mylanta, diphenhydramine, Carafate
Nystatin, diphenhydramine, hydrocortisone

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 [4, 6, 7]. Additionally, squamous cell cancer may present as a nonhealing or non-resolving ulcer, and biopsy of the ulcer should be considered [4].

Lichen Planus

Lichen planus is a chronic inflammatory condition most likely precipitated by an autoimmune response. Lichen planus affects approximately 1–2 % of the population, more often in those over age forty and a slight predilection in perimenopausal women [4, 6, 8]. In women with oral lichen planus, 25 % of them will also have concomitant involvement of the vulva and vagina [8]. 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 [8, 9]. 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 and avoiding irritating foods and tobacco products. Medium- to high-potency topical steroids are first-line therapy to treat symptomatic lichen planus [4, 8]. Clobetasol 0.05 % or fluocinonide 0.05 % is applied twice daily to lesions [8]. Topical calcineurin inhibitors such as pimecrolimus 1 % (Elidel) or tacrolimus 0.1 % (Protopic) can be effective for those patients that do not respond to topical steroids [8].

Glossitis

Geographic tongue also known as known as benign migratory glossitis affects 1–14 % of the population and is of unknown etiology [10, 11]. 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 includes bland foods and use of topical steroids triamcinolone 0.1 % (Oralone) or antihistamine mouth rinses which also can be used to help reduce tongue sensitivity [10].

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.

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Down's syndrome, Sjogren syndrome, Melkersson–Rosenthal syndrome, psoriasis, and geographic tongue have all been associated with fissured tongue [10].

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 [6, 10, 11]. 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 [10, 11]. 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 [10].

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 [10]. Nutritional deficiencies of iron, folic acid, riboflavin, niacin, and B_{12} are most often implicated [10]. Other possible etiologies include syphilis, candidal infection, amyloidosis, celiac disease, Sjogren syndrome, protein malnutrition, and xerostomia [9].

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 [12]. 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 [12]. 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 [13].

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 [12, 13]. 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 [14]. Gentle but thorough tongue cleaning using either a tongue scrapper or toothbrush should be added to

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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 [14]. 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 [12, 14].

Nasal sources are second in frequency to oral etiologies as causes of halitosis [12, 14]. 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 [14]. 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 [14]. 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 [14]. Trimethylaminuria is a rare genetic metabolic condition that can also produce a foul fishy odor [12, 13]. Diabetes is best known for its distinct sweet fruity odor [14]. GI causes are rarely implicated, though some sources have reported halitosis as a symptom related to *Helicobacter pylori* (*H.pylori*) infection [11, 12]. Studies investigating the reduction or elimination of halitosis in *H.pylori* patients after antibacterial therapy have not clearly demonstrated that the improvement in symptoms is not just a consequence of the simultaneous eradication of odor-producing oral bacteria [11].

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 [16]. 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 [16, 17]. In most cases, these disorders lack organic pathology, are self-limited, and resolve spontaneously [17]. 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. The TMJ may be imaged with a panoramic radiograph to screen for organic pathology [17]. More advanced imaging such as ultrasound, CT, or MRI should be ordered based on the findings of the panoramic film. Inter-incisal opening can be serially measured to assess for improvement. Underlying causes of TMJ disorders and treatments options are poorly understood. Behavioral, psychological, and structural factors all appear to contribute to the formation of TMJ disorders. The differential diagnosis of TMJ disorders should include, but is not limited to, osteoarthritis, rheumatoid arthritis, temporal arteritis, and claudication of the masticatory muscles. Oral habits such as frequent gum chewing or bruxism may aggravate or cause inflammation within the joint. Current literature indicates a need for high-quality randomized control trials comparing various treatment options. However, the one concept that all authors emphasize is that patient education be at the forefront of treating nonorganic and chronic TMJ disorders [16–18]. It is important for patients to understand that TMJ is

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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 [17, 18]. 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 [16–18]. 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. Referral for surgical evaluation is rarely indicated in the absence of organic pathology [17, 18].

Oral Cancer

Cancers of the oral cavity and oropharynx are the ninth most common cancer in the United States [19]. African-Americans have a higher incidence than Caucasians, and males have a slight predominance over their female counterparts [19]. Patients are typically over age 40 at time of presentation. Squamous cell carcinomas account for approximately 90 % of all oral cancers [4, 19]. Most commonly these lesions occur on the tongue, floor of the mouth, and vermillion border of the lower lip. The major risk factors for developing oral cancer are tobacco use of any kind and heavy alcohol consumption [2, 4, 19]. 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 [4]. Despite decreased smoking rates over recent years, the incidence of oral cancers has continued to rise. This increased incidence of oral cancers is largely explained by the rise in human papillomavirus (HPV)-positive cancers [20]. These cancers tend to occur more frequently in younger Caucasian males and have sexual behavior as the main risk factor [20]. Other potential risk factors for oral 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 % [4]. HPV-related oral cancers tend to have better survival rates and lower rates or recurrence [4, 20]. 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, 18]. 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 [19]. Any ulcer, white, red, or mixed lesion that is not resolving after removing any irritating precipitant such as tobacco, alcohol, and ill-fitting dental restorations, requires a biopsy to exclude malignancy [4, 19]. 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 periodic examination of the oral cavity especially in patients over age 40 with risk factors can help to reduce the incidence of oral cancers and increase earlier detection rates [21].

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Other Oral Lesions

Bony Tori

Tori are benign, nonneoplastic 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 [4, 19]. 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 [4, 19].

Mucocele

Mucoceles are benign fluid-filled sacs which result from disruption of a salivary duct gland secondary to mild local trauma such as biting. Most frequently they occur on the lower lip and are more prevalent in children and young adults [19]. 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 [4, 19]. 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 [4].

Pyogenic Granuloma

A pyogenic granuloma is an erythematous rapidly growing lesion that develops in response to local irritation, trauma, or increased hormone levels related to pregnancy [19]. 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 usually involves surgical excision and removing the local source of irritation. Recurrence is uncommon except in pregnancy. Pyogenic granulomas induced by pregnancy associated hormonal changes are more likely to spontaneously resolve following childbirth, and therefore observation alone may be an adequate treatment [19].

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Selected Disorders of the Ear, Nose and Throat

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Contents

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Adult Hearing Loss

General Principles

Hearing impairment affects over 28 million people in the United States. It is one of the most common disabilities of the adult population. Although hearing loss becomes more common in the aging population, it can also affect younger adults as a result of environmental exposures. Hearing loss is associated with decreased quality of life and can lead to, in severe cases, cognitive decline and depression [1, 2].

Pathophysiology

There are three different types of hearing loss: (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 [3]. This may be due to obstruction of the external auditory canal, impairment of the tympanic membrane function, or middle ear pathology [1]. 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, cholesteatoma, Eustachian tube dysfunction, myringosclerosis, otosclerosis, and glomus tumors [4].

Sensorineural hearing loss is due to dysfunction of the inner ear or neural pathways to the auditory cortex. Sensorineural hearing loss usually begins at high frequencies and progresses to lower frequencies [1]. This may occur bilaterally or unilaterally and is more commonly found in adults. Bilateral sensorineural hearing loss most commonly is found in the elderly, referred to as presbycusis [4]. Noise trauma due to exposure to occupational, recreational, and accidental noise also results in sensorineural hearing loss. Prolonged and chronic noise exposure to levels of greater than 85 dB can lead to permanent and irreversible hearing loss [2]. 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 progressing bilateral sensorineural hearing loss with poor speech discrimination as well as vertigo and disequilibrium [4]. Infections such as meningitis, herpes, mumps, syphilis, and tuberculosis may also lead to hearing loss [2]. Unilateral sensorineural hearing loss may also 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, Meniere's disease, acoustic neuromas, or other cerebellopontine-angle tumors, or it may be considered idiopathic [4]. Certain noise exposures (gunfire) may also cause unilateral hearing loss [2].

Evaluation and Diagnosis

Hearing loss may simply be identified by asking, "Do you have trouble hearing?" Other hearing loss screens 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 [1, 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. Finally, evaluate the head, neck, and cranial nerves if clinically indicated [2, 4].

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 [3]. This test may evaluate hearing from frequencies of 250–8000 Hz [2]. 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 [5].

Treatment

If a concern of hearing loss is identified and proper equipment is not available in the primary care office, specialty referral to audiology and/or otolaryngology is indicated. Counsel on and eliminate environmental noise and ototoxic agents if possible. Intervention is important, not only for hearing improvement but also for social and emotional function, as well as for communication and cognition [1].

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. Surgical implants are an option for those with severe cochlear (sensorineural) hearing loss.

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, 2].

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 [2].

Pediatric Hearing Loss

General Principles

Hearing loss is the most common neurological birth defect and the fourth most common developmental defect in the United States [6, 7]. Pediatric hearing loss can have a profound impact on growth and development of the infant and child to include adversely affecting speech and language development, academic success, visual reception, fine motor skills, and social and emotional development. Early intervention may prevent long-term impacts of pediatric hearing loss [7, 8].

Pathophysiology

Hearing loss in the neonate or child can be classified as congenital or acquired. Of the congenital etiologies, it can be further classified as either (1) syndromic or nonsyndromic or (2) autosomal recessive, autosomal dominant, or X-linked [7]. Of the acquired cases of hearing loss, approximately half are considered environmental and half idiopathic [8]. Environmental risk factors to the neonate include cytomegalovirus, rubella, measles, syphilis, or 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. Ear malformations are considered nonsyndromic genetic or hereditary causes of hearing loss. The most common inner ear malformation is the vestibular aqueduct enlargement [7, 8].

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 (ABR) test. The OAE is largely used as the initial screening for most newborns [6]. It allows for individual ear

testing at any age. It is an effective screen for middle ear pathology and for moderate to severe hearing loss [9]. Passing the OAE demonstrates functioning middle ear; however, it does not test the eighth nerve [7]. Results of this test may be interrupted by middle ear fluid, ear canal debris, or external environmental noise [6]. The ABR test is often used as a follow-up screening exam if the OAE is failed; however, the ABR may be used as an initial screen and is often used as such in the settings of neonates in the intensive care unit. The ABR is considered a superior evaluation of the auditory system and better detects auditory neuropathy. It requires a sleeping or quiet infant as motion can cause artifact [6, 9]. The Joint Committee on Infant Hearing encourages that all neonates undergo hearing screening. If the neonate does not pass, then rescreen and refer for further evaluation by the age of 3 months. Any infant with hearing loss should have intervention by 6 months of age [10, 11].

If the initial newborn screening exams are passed, it is still important to continually evaluate pediatric patients for potential hearing impairment. This may be realized during well exams if developmental milestones are missed, especially speech and language development. It is important to address any parental concerns during these visits. If the neonate has risk factors of hearing impairment, at least one diagnostic audiology assessment should be completed by age 24–30 months. Risk factors are listed in Table 1 [7, 9, 10, 11].

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 [7]. 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 [7, 9, 10, 11].

Further imaging and laboratory testing may be indicated. Imaging such as a computed tomography (CT) scan may assess the temporal bone. A magnetic resonance imaging (MRI) may further evaluate the brain and internal auditory canal.

Table 1 Risk factors for infant and child hearing loss [7, 9, 11]

In utero infectious exposures or postnatal infections associated with hearing loss: cytomegalovirus infection, herpes, rubella, syphilis, toxoplasmosis, meningitis
Syndromes associated with progressive hearing loss
Craniofacial abnormalities
Neurodegenerative disorders
Head trauma
Extracorporeal membrane oxygenation (ECMO)
Chemotherapy
Caregiver concern
Family history of hearing loss
Identification of syndromes related to hearing loss
Genetic testing related to hearing loss
Speech and language delay
Neonatal intensive care for greater than 5 days
Exposure to ototoxic medication (gentamycin, tobramycin, loop diuretics, etc.)
Hyperbilirubinemia requiring exchange transfusion
Chronic otitis media with effusion
Excessive noise exposure
Hypoxia requiring respiratory support

Labs may be completed based on history and physical exam findings [7, 9, 10].

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 [11].

Tinnitus

General Principles

Tinnitus is the perception of sound within the ears or head without an objective external stimulus. The noise has been described as ringing, buzzing,

Table 2 Risk factors for tinnitus [12, 14]

Hearing loss
Exposure to high levels of recreational and occupational noise
Obesity
Alcohol use
Smoking
Arthritis
Hypertension
Ototoxic drugs: salicylates, quinine, aminoglycoside antibiotics, platinum-based antineoplastic agents
Otologic diseases: otosclerosis, Meniere's disease, vestibular schwannoma (acoustic neuroma)
Anxiety
Depression
Dysfunction of the TMJ
Hyperacusis (loud noise sensitivity)

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. It can have great effect on the quality of life for those who suffer from tinnitus [12, 13].

Pathophysiology

There is no clear etiology of tinnitus; however, there are some known risk factors which are outlined in Table 2. Tinnitus is most notable in patients who have been exposed to hazardous levels of industrial, recreational, or military-related noise [12]. Other underlying associations to tinnitus include nerve 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 [12, 14].

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 [13, 14].

Evaluation and Diagnosis

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 [12, 13]. Assess the character of the tinnitus: (1) subjective versus objective, (2) location and quality, and (3) distinguish chronicity (chronic is considered at least 6 months duration). Subjective idiopathic tinnitus is the most commonly diagnosed type of tinnitus [12]. There are several questionnaires to evaluate tinnitus to include the "Tinnitus Handicap Inventory" and the "Tinnitus Functional Index" [12]. Evaluate for any associated hearing loss and tympanic membrane dysfunction [13].

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 provider [12].

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 [12, 13]. 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 [12].

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 [12].

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 [12, 13].

Unfortunately, there is no single effective treatment regimen to cure or significantly alleviate tinnitus. It is important to treat or eliminate any underlying risk factors. Any surgical otologic disorders should be evaluated by otolaryngology.

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 [13].

Salivary Gland Inflammation and Salivary Stones

General Principles

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, or sialadenitis, are most common in the major salivary glands. Inflammation may be acute or chronic, and the inflammation occurs due to viral, bacterial, autoimmune, or neoplastic etiologies. These conditions can also lead to salivary stone formation which will further enhance the inflammation in some cases [16].

Pathophysiology

Acute bacterial sialadenitis is most often seen in the parotid gland in medically debilitated patients. Debilitation and dehydration may lead 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 influenza [15, 16].

Acute viral sialadenitis is most commonly found in the setting of mumps in children aged four through six. Other viral causes include Cytomegalovirus, Lymphocytic Choriomeningitis virus, Coxsackie virus A, echo virus, and parainfluenza virus type C [16].

Chronic sialadenitis is characterized by repeated episodes of pain and edema. Noninfectious etiologies of chronic sialadenitis include autoimmune diseases, previous irradiation, Sjogren's syndrome, and paucity of salivary flow with resultant stones or salivary duct strictures. Infectious etiologies include Mycobacterium, Toxoplasma, and Actinomyces species [16].

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 during 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 [15].

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 or strictures. 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 and biopsy is essential for further diagnosis. A CT scan with contrast or MRI may also be used to identify the mass's characteristics [15].

Ultrasound is the primary imaging modality for evaluation of sialadenitis. Ultrasound can help to identify characteristics of the gland as well as to identify any associated stones [16].

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 mumps treatment is supportive. It is important to hydrate and control the pain as well as promote oral hygiene. Mumps usually resolves spontaneously within weeks [15].

Any stones contributing to acute or chronic sialadenitis may need surgical removal if not easily removed through the duct orifice.

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 [15].

Xerostomia

General Principles

Xerostomia is the subjective sensation of dry mouth. It is a common condition in the elderly, affecting up to 57 % of those greater than age 65 [17]. Major and minor salivary glands produce the saliva, which is composed of electrolytes, organic compounds, and water. The salivary glands continually change the production of saliva based on flow rate, blood supply with available substances, and stimuli. Saliva aids in digestion, prevents dental caries, and protects mucosal surfaces. Saliva also contributes to the sensation of thirst in times of dehydration [18].

Pathophysiology

Xerostomia can occur with the reduction in the quantity, flow rate, or composition of the saliva produced. In some cases, xerostomia may occur despite normally produced saliva. Xerostomia can adversely affect speaking, chewing, and swallowing. Prolonged dry mouth can lead to tooth decay and reduced quality of life [19]. There are several causes of xerostomia such as dehydration, poor nutritional status, head or neck radiation, chemotherapy, salivary gland aplasia, Sjögren's syndrome, depression, smoking, and a variety of medications, which are listed in Table 3 [17].

Evaluation and Diagnosis

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.

Table 3 Medications contributing to xerostomia [17]

Anticholeinesterase (ACE) inhibitors
Alpha or beta blockers
Anticholinergics
Antidepressants
Antipsychotics
Anxiolytics
Calcium channel blockers
Diuretics
Muscle relaxants
Sedatives
Antiepileptics
Antiparkinsonisms
Cytotoxics
Antihistamines
Tricyclics

On exam, the mucosal surfaces may be dry and the tongue swollen and dry [17].

Treatment

Treatment is aimed at identifying the offending agent and either eliminating it or treating it. 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. Avoid food and drinks such as alcohol, sugar, and caffeine which may lead to dry mouth or dental caries [17].

Topical treatments, saliva stimulators, and saliva substitutes are also available. Sugar-free chewing gum or candy can promote salivation [17]. Oxygenated glycerol triesters (OGTs) are saliva substitute sprays that have been shown to be effective at improving dry mouth [19]. Medication which may stimulate saliva production includes Pilocarpine or Cevimeline drops [17].

Hoarseness

General Principles

Hoarseness (or dysphonia) is a term used to describe a symptom or sign of altered voice quality [20]. The change in voice may be an alteration in quality, pitch, loudness, or may be described as breathy, strained, rough, or raspy [20, 21]. It is a common problem in the US 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 [20].

Table 4 Etiologies of hoarseness (or dysphonia) in the adult population [21]

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)

Pathophysiology

The larynx houses the vocal cords, 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 [21].

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 [21]. Table 4 outlines details of each of these categories.

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, or odynophagia is important and may lead to more serious underlying causes of hoarseness [20, 21].

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, or weight loss may be more concerning for serious etiologies such as malignancies. Stridor may indicate airway obstruction due to mass [21].

Laryngoscopy may be performed at any point in time. Different recommendations exist as to when direct visualization is required ranging from after 2 weeks to after 3 months of persistent hoarseness [20, 21]. 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 obacco or alcohol use, a neck mass, hemoptysis, dysphagia, odynophagia, neurological symptoms, unexplained weight loss, aspiration of a foreign body, persistent symptoms after surgery or if the hoarseness significantly impairs the quality of life of the patient, then visualization is more urgent [20].

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 [20].

In cases of pediatric hoarseness, it is generally indicated for the patient to be referred to otolaryngology and speech and language pathology early [22].

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, or reflux. If reflux is suspected, a 4 week trial of high-dose PPI for 3–4 months is warranted; however, if there are no other signs of reflux, treatment for such is not recommended. Likewise, antibiotics are usually not indicated in treating hoarseness [20, 21]. 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 [21]. Oral corticosteroid to treat hoarseness is not recommended [20]. 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 [20, 21].

Surgery may be indicated for any findings of benign or malignant masses, glottic insufficiency, or if airway obstruction is a risk [20, 21].

Prevention

The patient should be counseled on avoidance of triggers such as tobacco smoke, environmental irritants or allergens, and vocational abuse of the voice [20].

Epistaxis

General Principles

Epistaxis is a common condition that can affect up to 60 % of the general population [23]. Up to 9 % of the pediatric population experiences recurrent epistaxis. Epistaxis is generally categorized as anterior (more common) or posterior (less

Table 5 Local and systemic causes of epistaxis [23–25]

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	

common but more severe). Anterior epistaxis generates from either Kiesselbach's plexus or the anterior inferior turbinate [24]. Posterior epistaxis results from bleeding of the posterior edge of the nasal septum of the nasopharynx.

Pathophysiology

The etiology of epistaxis can be divided into two general causes: local or systemic. Local causes refer to specific complications to the nasal mucosa. Systemic causes refer to more systemic diseases causing epistaxis to be more likely [23]. See Table 5 for a list of local and systemic causes of epistaxis.

In children, the most common etiology of anterior epistaxis is trauma (usually nose picking). 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 Willenbrand disease, hemophilia, warfarin use, liver diseases leading to coagulopathy, or drug-related thrombocytopenic purpura [25].

Evaluation and Diagnosis

Anterior epistaxis is generally obvious to the examiner, and blood loss is usually not significant. 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 [23]. 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 [24].

The physical exam may be performed with the aid of a vasoconstrictor spray or gauze soaked in a vasoconstrictor. This in combination with an anesthetic may be helpful during the physical exam to successfully identify the source of bleeding [25].

Treatment

Because 90 % of epistaxis cases are anterior, most cases of epistaxis are treated successfully with conservative therapies [24]. 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 [23, 24]. It is important to tilt the head forward, not backward, in order to avoid pooling of the blood, which can lead to airway obstruction [23]. 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 [25]. Avoid cauterizing bilaterally due to risk of septal necrosis and perforation. If bilateral cauterization is needed, it is optimal to perform cauterization 4–6 weeks apart [24, 25].

If this initial management is unsuccessful, nasal packing may be an effective next step. 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 [23]. 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 is 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. Antistaphylococcal antibiotic (oral or topical) may be considered as prophylactic therapy [24].

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 [23–25].

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 [25, 26].

Foreign Bodies in the Ear and Nose

General Principles

Foreign bodies lodged in the ear and nose is a problem commonly seen in children and patients with mental handicaps [27]. At times, it can be difficult to diagnose as the object placement may not have been observed by the parent or caregiver [28]. Common foreign bodies found in the ear or nose include beads, rubber erasers, toy parts, pebbles, food, marbles, and button batteries [28, 29].

Pathophysiology

Although a 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 or anterior to the middle turbinate [28, 29].

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 [28].

Evaluation and Diagnosis

A nasal cavity foreign body may be asymptomatic; however, it may also present as unilateral, malodorous, mucopurulent nasal discharge. Intermittent epistaxis may also be present. It may cause pain or be painless [29]. If left for a prolonged period of time, it can lead to ulceration or erosion of the mucous membrane.

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 [28]. Anesthesia may also be accomplished with a topical spray such as 4 % lidocaine [27]. Anterior rhinoscopy can be performed with the use of a fiberoptic nasopharyngoscope or a zero-degree rigid endoscope [29].

A foreign object in the ear may also be asymptomatic or an incidental finding on exam. Symptoms can include otitis, hearing loss, or a sense of ear fullness [28]. It is important to appropriately

visualize the object in order to decrease trauma. If it is not easily visualized or if ear anesthesia is necessary, it may be necessary to refer to a specialty physician. Topical anesthesia of the ear is generally not successful [27].

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 [27].

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. A balloon tip catheter may be used by lubricating the balloon tip, passing the tip past the foreign body, inflating, and then pulling forward [28]. Of course, asking the patient to blow his/her nose with the opposite nostril occluded is also an option. Positive pressure may be performed on babies by occluding one nostril and blowing air through the mouth [27]. 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 for small objects closer to the tympanic membrane [27]. 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. 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 [28].

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Family Medicine
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Hypertension

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General Principles

Hypertension is the most commonly seen condition in adult primary care practices. It affects one in three American adults over the age of 18, with women and men being nearly equally affected [1]. Data from the Framingham Heart Study have shown that patients who are normotensive at 55 years old still have a 90 % lifetime risk for developing hypertension [2]. Fortunately, treatment of hypertension reduces the risk of heart failure, stroke, myocardial infarction, chronic kidney disease, and cognitive decline. Left untreated, hypertension may lead to vascular and renal damage, which with time could become treatment resistant [3]. The percentage of people who know they have hypertension, who are treated, and who have controlled blood pressure (BP) has increased. From 2005 to 2010, nearly 82 % of adults with hypertension were aware of their status (up from 75 % in prior years), and approximately 75 % were taking medication. Nearly 53 % of these patients had controlled BP [4, 5].

Men and women between the ages of 55 and 64 are equally likely to have high BP with nearly 52 % of the population affected. Prior to this age, men are more commonly affected, and after these ages, more females are affected. Black women most commonly have hypertension (43 %), with black men following (40 %). Approximately 30 % of white men have high BP whereas 27 % of white women are affected. About 26 % of Mexican American men and women have hypertension [4, 5].

Lifestyle modifications to lower BP include weight loss (if overweight), increased physical activity, alcohol use only in moderation, reduced sodium intake, and the Dietary Approaches to Stop Hypertension (DASH) eating plan [6]. Multiple pharmacological treatments are available including diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), calcium channel blockers, and beta-blockers. Unfortunately, many patients do not fully adhere to the treatment plan or self-adjust their regimens based on side effects of their medications. Clinicians also have a tendency to tolerate less than adequate BP control and not titrate BP-lowering medications. This clinical inertia plays an important role in suboptimal BP control. Overall, it is the physician's challenge to develop a plan with patients that will effectively control their BP, reduce cardiac risk factors, and manage comorbidities (e.g., diabetes) while minimizing side effects and maintaining quality of life. Treatment and the plan of care should include the patient's needs and preferences [2].

Detection and Diagnosis

The United States Preventive Services Task Force (USPSTF) recommends screening all adults over 18 for hypertension [7]. While the USPSTF previously made no recommendation as to screening interval, the Joint National Committee (JNC)-7 recommended screening adults every 2 years if BP was recorded as less than 120/80 mmHg and every 1 year for systolic BP 120–139 mmHg or diastolic BP 80–90 mmHg [6]. Recently, the USPSTF published recommendations for annual screening for adults 40 years and older

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Table 1 Classification of blood pressure levels for adults

BP classification	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Management
Normal	<120	<80	Healthy lifestyle recommendations to maintain optimal BP
Pre-hypertension	120–139	80–89	Healthy lifestyle recommendations to try to prevent hypertension.
Stage 1 hypertension	140–159	90–99	Healthy lifestyle recommendations plus BP-lowering medication(s)
Stage 2 hypertension	≥160	≥100	

Source: Joint National Committee-7

and those at increased risk for high BP. Persons deemed at increased risk include those who have high-normal BP (130–139/85–89 mmHg), are overweight or obese, or are African American. Adults ages 18–39 years with normal BP (<130/85 mmHg) who do not have other risk factors should be rescreened every 3–5 years [8].

The diagnosis of hypertension should be based on at least two separately recorded elevated BP recordings. The finding of an elevated BP at an initial visit should be confirmed at a follow-up visit, preferably with at least two BP recordings separated by at least 1 min each time [9]. In a patient with a single greatly elevated BP reading in the office setting who already has hypertensive-related target organ damage, the diagnosis may be made without follow-up readings. BP should be recorded with the auscultatory or oscillometric method in a standardized fashion. Patients should be seated quietly for at least 5 min in a chair with their feet on the floor and arm supported at heart level. An appropriate-sized cuff (cuff bladder encircling at least 80 % of the arm) should be used to ensure accuracy [6]. Additionally, caffeine and nicotine should not be ingested within the 30 min prior to measurement. Ideally, ambulatory BP monitoring (see subsequent section) should be used to confirm the diagnosis [8], primarily to exclude white-coat hypertension.

BP level can be classified into one of several categories, as shown in Table 1. The BP category into which a patient falls can help guide treatment.

Evaluation

The evaluation of patients with newly diagnosed hypertension has three main goals: (1) assess for comorbid cardiovascular disease (CVD) risk factors, (2) investigate for potential secondary causes of hypertension, and (3) determine if the patient has any target organ damage. These goals can be addressed with a thorough medical history, physical exam, laboratory evaluation, and, if necessary, diagnostic procedures.

Medical History

The provider should ask about previously elevated BP measurements, CVD risk factors (Table 2), symptoms of or diagnosis of secondary causes of hypertension (see below), medication (including supplement) use, and family history of hypertension and cardiovascular disease.

Physical Exam

Each patient diagnosed with hypertension should have a physical exam including more than one BP recording verified with recording in the contralateral arm in both the standing and sitting position. The

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Table 2 Major cardiovascular disease risk factors

Hypertension
Cigarette smoking
Obesity (body mass index >30)
Physical inactivity
Dyslipidemia
Diabetes
Microalbuminuria or GFR <60 mL/min
Age (>55 men or >65 women)
Family history of premature cardiovascular disease (1st degree male relative <55 years, female <65 years)

Source: JNC-7

Table 3 Drugs that may cause BP elevation

Drug	Common examples
Estrogen	Oral contraceptives, hormone replacement therapy
Herbals	Ephedra, ginseng
Illicit drugs	Amphetamines, cocaine
Non-steroidal anti-inflammatories	Ibuprofen, Naproxen
Psychiatric agents	Fluoxetine (Prozac), Lithium, Tricyclic Agents (TCAs)
Steroids	Prednisone
Sympathomimetics	Over-the-counter nasal decongestants

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 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 (8) a neurological evaluation.

Laboratory Tests and Diagnostic Procedures

Baseline laboratory tests may be helpful for the initial evaluation and are also important before initiating treatment. Recommended tests include serum potassium and sodium levels, blood urea nitrogen, and creatinine level. An electrocardiogram, 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. Tests such as a chest radiograph or echocardiogram are only recommended if indicated based on findings from history, physical exam, or ECG.

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. Diets high in salt and alcohol can contribute to elevated BP. Many medications can cause elevation of BP as well (Table 3). A trial of potentially offending medications (if possible), or a change in diet, may be warranted before embarking on pharmacological treatment.

The initial history, examination, and laboratory tests on rare occasions may reveal a potential secondary cause of hypertension which can be investigated (Table 4). The most common secondary causes of

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Table 4 Secondary causes of hypertension in adults

Aldosteronism
Atherosclerotic renal artery stenosis
Cushing Syndrome
Fibromuscular dysplasia
Obstructive sleep apnea
Pheochromocytoma
Renal Failure
Renal parenchymal disease
Thyroid dysfunction

hypertension vary by age-group [10]. Among children, renal parenchymal disease and coarctation are most common, while among middle-aged adults, obstructive sleep apnea and aldosteronism are the most common. Further investigation for secondary causes should be completed in a stepwise fashion based on level of suspicion or concern [10].

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 % [11]. These data support the importance of treating patients to not only bring BP down but more importantly to prevent the morbidity and mortality associated with hypertension.

The panel members appointed to the Joint National Committee 8 (JNC 8) recently provided an evidence-based update to BP treatment goals. Per their report, in the general population aged ≥60 years, pharmacological treatment should be initiated to lower BP at systolic BP ≥150 mmHg or diastolic BP ≥90 mmHg and treat to a goal systolic BP <150 mmHg and goal diastolic BP <90 mmHg. 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 ≥140 mmHg and treat to a goal of <140 mmHg, and grade A recommendation is to initiate pharmacological treatment to lower BP at diastolic BP ≥90 mmHg and treat to a goal <90 mmHg. In the population aged ≥18 years with chronic kidney disease (CKD) or diabetes, the recommendation is to initiate pharmacological treatment at systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg and treat to goal <140/90 mmHg [12].

Nonpharmacological Interventions

Lifestyle recommendations should be part of the management plan for all patients with hypertension. These recommendations include the DASH eating plan, reduced sodium intake, exercise, alcohol reduction, and weight loss if overweight (Table 5). For overall cardiovascular disease risk reduction, all patients who smoke should be counseled about smoking cessation and provided 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 [13].

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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 mmHg
Exercise	Regular aerobic activity at least 30 min per day	4–9 mmHg
Reduced dietary sodium intake	Maximum 2400 mg (ideally 1600 mg) of sodium daily	2–8 mmHg
Moderate alcohol drinking	Maximum 2 oz ethanol per day for men; maximum 1 oz per day for women	2–4 mmHg
Weight loss	Achieve/maintain BMI of 18.5–24.9 kg/m2	5–20 mmHg

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 [14].

Some research has shown increased BP to be positively correlated to more than 2 oz/day of alcohol. Therefore, it is important to limit alcohol intake [15]. Alcohol should be limited to no more than 1 oz or 30 mL ethanol/day for women and no more than 2 oz (60 mL)/day for men [8].

Pharmacological Treatment

When deciding on pharmacological 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 taken into account.

In the general nonblack population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, calcium channel blocker (CCB), ACE inhibitor, or ARB. In the general black population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic or CCB. In the population aged $\geq$18 years with 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 [16].

The main objective of hypertension treatment is to attain and maintain goal BP. 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 [12] (Fig. 1).

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

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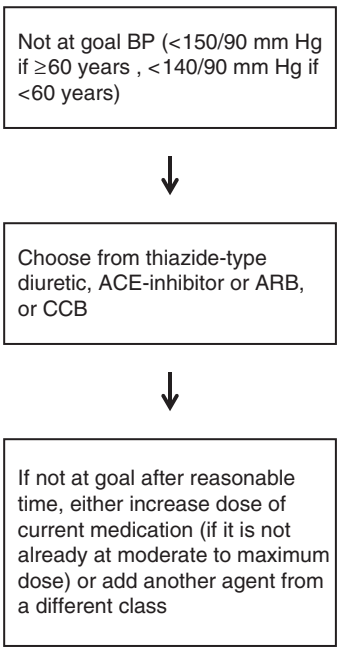

Fig. 1 Evidence-based simplified algorithm for hypertension treatment

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 [17].

ACE Inhibitors

ACE inhibitors block the conversion of angiotensin I to angiotensin II, resulting in decreased aldosterone production with subsequent increased 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.

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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 the 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. The 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. Beta1-receptors are predominant in the heart (and 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.

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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 caused. 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.

Follow-up and Ongoing Care

After initiating therapy, most patients should be seen monthly until BP control is met. More frequent visits should be utilized for patients with significant comorbidities or with stage 2 hypertension until BP goals are met. Once goals are met, follow-up can be spaced out to every 3–6 months. Laboratory evaluation including serum creatinine and potassium should be obtained at least 1–2 times/year [6].

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Resistant Hypertension

Resistant hypertension occurs when BP remains above goal even with adherence to a combination of at least three optimally dosed antihypertensive agents of different classes. Management of resistant hypertension includes assessing adherence, readdressing lifestyle modifications, working up potential secondary causes, and optimizing drug regimens [17, 18].

It is important to revisit drug adherence in patients with resistant hypertension. Patients may discontinue the use of some agents due to side effects, multiple daily dosing, and/or financial expense. When possible, it is important to simplify the patient's medication regimen. Once-daily dosing and single-pill combinations improve patient's adherence to antihypertensive medications [19]. Discussing side effects with the patient may increase both their understanding of the medication as well as their adherence to the agents. Volume overload can often play a role in resistant hypertension, and for this reason, unless contraindicated, all patients should be treated with a regimen that includes at least one diuretic.

It is also important to ensure accurate BP measurements when investigating resistant hypertension. Careful attention should be paid to measurement technique. Approximately one-third of patients with suspected resistant hypertension will actually have normal BP on ambulatory blood pressure monitoring. Therefore, evaluation of the patient with potentially resistant hypertension should include out-of-office monitoring to rule out white-coat effect [18].

Home and Ambulatory Blood Pressure Monitoring

With ambulatory BP monitoring (ABPM), the patient wears a monitor that is preprogrammed to measure and record the BP multiple times over 24 h. Recent recommendations from the USPSTF state that ABPM should be used to confirm high BP prior to diagnosis and treatment of hypertension, unless immediate therapy is indicated [8]. By providing confirmatory measurements in the ambulatory setting, overdiagnosis and overtreatment can be avoided.

Home blood pressure monitoring (HBPM) also can be useful in confirming the diagnosis of hypertension if done in a systemic way after BP cuff is confirmed to be the appropriate size, correct technique is used, and the device is accurate. HBPM may also improve patient's compliance with treatment and awareness of their control.

Hypertensive Emergency

A hypertensive emergency is described as a severe elevation in BP accompanied by evidence of impending or progressive target organ dysfunction [6]. Clinical manifestations of target organ damage usually involve derangements in the neurological, cardiac, or renal systems. The patient with hypertensive emergency may present with encephalopathy, pulmonary edema, myocardial infarction, or unstable angina.

The most common origin of hypertensive emergency is an abrupt increase in BP in patients with chronic hypertension, most often as a result of medication noncompliance [20]. Hypertensive emergency may be related to medication effect. Examples include withdrawal syndrome from antihypertensives including clonidine and beta-blockers as well as stimulant intoxication with cocaine, methamphetamine, and phencyclidine (PCP). Pheochromocytoma is a rare cause of hypertensive emergency.

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 neurological 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 BP by 10–15 %, but by no more than 25 %, within the first hour and, if the patient is then stable, to 160/100–110 mmHg over the ensuing 2–6 h [6]. Potential medication choices for treatment include hydralazine, labetalol, methyldopa, and nitroglycerin.

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Ischemic Heart Disease

Anthony J. Viera and Ashley Rietz

Contents

General Principles

Ischemic heart disease (IHD) refers to the condition of inadequate blood supply to the myocardium. It is also commonly referred to as coronary heart disease or coronary artery disease. Each year about 600,000 Americans have their first myocardial infarction (MI) with more than 300,000 experiencing a subsequent event [1]. In 2010, the total number of people affected by IHD was estimated to be 17 million [2]. While deaths from IHD have declined since 2000, it remains the leading killer of both men and women [3, 4]. In addition to the loss of life, IHD has a large financial impact. The National Heart, Lung, and Blood Institute estimates a loss of 177 billion dollars in 2010 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 chest pain is ultimately what leads to the diagnosis in most instances. 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.

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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 a myocardial infarction. However, it is important to note that few cases of chest pain seen in the primary care setting are cardiac in nature. Most such patients have musculoskeletal (36 %), esophageal (19 %), or anxiety-related causes (at least 8 %) [5]. 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 classically described as a sensation of pressure or heaviness located in the center or left side of the chest. It is brought on by exertion and relieved by rest. Its onset is typically not abrupt and lasts for only a few minutes. Angina can be specified further by the level of exertion needed prior to onset. Stable angina typically occurs during strenuous or prolonged typical activity [2]. 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.

It is important to note that "nonanginal" pain does not mean that IHD is not the cause, only that the pain is much less characteristic. With the combination of the type of chest pain (typical angina, atypical angina, nonanginal) and a patient's age and sex, the pretest probability of flow-limiting IHD can be estimated (Table 1) [6].

While these criteria are helpful in estimating the pretest probability of IHD, it is worth noting that in the WISE (Women's Ischemic Syndrome Evaluation) study, women ultimately diagnosed with IHD did not have typical angina 65 % of the time [7]. Additionally, some patients lack the chest discomfort and are thus characterized as having silent ischemia.

Other important symptoms to inquire about include pain radiating to the arm(s) or jaw, epigastric pain, dyspnea, and any association of the pain with nausea, diaphoresis, or syncope [8]. Such clinical features increase the probability of a myocardial infarction in patients presenting with chest pain. Interestingly, pain radiating to both is the clinical feature that has the strongest positive likelihood ratio (approximately 7) for acute MI [9]. Pain that is pleuritic, sharp, or positional tends to lower the likelihood of MI as the etiology [10].

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.

Acute coronary syndrome (ACS) refers to unstable angina, non-ST segment elevation myocardial infarction (NSTEMI), and ST segment elevation myocardial infarction (STEMI). When angina occurs at rest and lasts more than 20 min or newly occurs with minimal exertion, it is categorized as unstable angina [2]. Additionally, 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 deemed unstable angina [11]. The historical features of unstable angina overlap with those of NSTEMI and STEMI. For example, rest angina lasting longer than 20 min is associated with both types of acute MI [11]. For this reason, unstable angina and MI cannot be differentiated by history alone. The use of electrocardiogram and cardiac

Table 1 Estimating pretest probability of ischemic heart disease [6]

	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

biomarkers (discussed below) is essential to distinguishing among these clinical entities.

Physical Exam

Generally speaking, the physical exam is not typically 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.

A third heart sound or pulmonary crackles on auscultation also would be concerning for possible MI [9]. Tenderness or reproducibility of chest pain on chest wall palpation argues against IHD as a diagnosis but does not necessarily rule it out [10].

Electrocardiogram and Biomarkers

The electrocardiogram (ECG) is a critical component of the evaluation of IHD, whether stable or possible acute coronary syndrome. 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 [8]. 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 [12]. 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 195,000 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 possible ACS. They are not part of the evaluation of patients with stable IHD. Cardiac troponins are biochemical markers of active or recent myocardial damage. Increases in cardiac biomarkers, notably cardiac troponin (I or T) or the MB fraction of creatinine kinase (CKMB), signify myocardial injury leading to necrosis of myocardial cells. 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 [13]. As a result, cardiac biomarker elevations cannot be utilized in isolation to make a diagnosis of MI. The preferred cardiac biomarker is troponin, which has high clinical sensitivity and myocardial tissue specificity [14]. 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. 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.

Stress Testing and Cardiac Imaging

In the evaluation of a patient with possible stable IHD, the first step before ordering or conducting a stress test is to decide whether it will be helpful. For patients with a low pretest probability (Table 1), a stress test is not diagnostically helpful. The sensitivity and specificity of a standard exercise tolerance test varies depending on the definition of disease (e.g., >70 % stenosis) but in general has a sensitivity of approximately 50–65 % and specificity of approximately 75–85 % [15]. 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 posttest probability sufficiently. Such patients should be considered for diagnostic coronary angiography (catheterization).

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.

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 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 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 [11]. A risk assessment tool can be used to predict the patient's risk of recurrent ischemia or death following an ACS event. The Thrombolysis in Myocardial Infarction (TIMI) risk score is a scoring system for UA and NSTEMI that incorporates seven variables upon hospital admission and has been validated as a reliable predictor of subsequent ischemic events (Table 2) [11].

For patients presenting with a STEMI with symptom onset within the prior 12 h, reperfusion therapy should be considered [16]. 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 [16]. 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 benefit of an early invasive strategy for patients initially presenting with NSTEMI or UA is less certain. A meta-analysis was inconclusive in regard to survival benefit associated with early (typically $<$24 h) versus delayed invasive strategy in patients presenting with NSTEMI [17]. However, early invasive coronary angiography is recommended in NSTEMI/UA patients who have refractory angina or hemodynamic or electrical instability [18]. Early invasive strategy is reasonable for higher-risk NSTEMI/UA

Table 2 The Thrombosis and Myocardial Infarction (TIMI) risk score for UA/NSTEMI [11]

Baseline characteristics	TIMI risk score (points)	Rate of composite endpoint (%)[a]
1 point for each of the following: Age $\geq$ 65 years At least 3 risk factors for IHD[b] Prior coronary stenosis $\geq$ 50 % ST segment deviation At least 2 anginal events in the last 24 h Use of aspirin in the 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

patients previously stabilized who do not have serious comorbidities (e.g., liver or pulmonary failure, cancer) or contraindications to the procedure [18].

Antithrombotic Agents. Antiplatelet therapy is a foundation in the management of ACS because it reduces the risk of thrombosis [18]. 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 162–325 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 [16, 18]. P2Y12 receptor antagonists frequently used in the management of ACS include clopidogrel (Plavix), prasugrel (Effient), and ticagrelor (Brilinta) [19–22]. 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 [18].

Anticoagulants. 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 [11, 16].

Beta-Blockers. For patients presenting with UA, 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 [11]. 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 [23]. For patients who are unable to take beta-blockers and experience recurrent ischemia, consideration should be given to starting a nondihydropyridine calcium channel blocker (i.e., verapamil or diltiazem) [11, 16].

Renin-Angiotensin Inhibitors. 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

Table 3 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 mmHg for most patients	Beta-blocker recommended as part of regimen for post-MI patients
Cholesterol-lowering medication	Statin therapy	Use at least moderate 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

fraction (LVEF) $\leq$ 40 % [11, 16]. ACE inhibitors have been shown to reduce mortality in a broad spectrum of patients following MI, including those with and without LV dysfunction [24–29]. Patients with stable CAD who are not medically optimized (i.e., cannot tolerate a beta-blocker or statin), who are not able to be revascularized, and/or who have poorly controlled diabetes have shown mortality benefit with continued treatment with ACE inhibitors [30]. 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 Therapy. Statin (HmG-CoA reductase inhibitor) therapy is recommended for all patients presenting with ACS who have no contraindications [11, 16]. 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 [31]. Statin therapy is beneficial following ACS even in patients with baseline low-density lipoprotein cholesterol levels of <70 mg/dL [11, 16]. 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 event [32]. Lower-dose statins can be considered if patients are >75 years old or if patients cannot tolerate high-intensity statins.

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 "ABCs" of management are shown in Table 3.

Antiplatelet Medication. Low-dose aspirin (typically 81 mg) is recommended for all patients for secondary prevention unless it is contraindicated (e.g., allergy) or poorly tolerated [2]. 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.

Blood Pressure Lowering. 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 mmHg systolic and/or >90 mmHg 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 mmHg prior to initiation of therapy in patients 60 years and older. See the chapter on "▶ 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 [32]. The LDL goals seen in previous guidelines are no longer recommended. Consider at least a moderate-dose statin in patients older than 75 [32]. Statins are the preferred treatment, but for patients who do not tolerate them, a bile acid sequestrant or niacin (or both) are reasonable alternatives. Fibrates can be prescribed for patients with elevated triglycerides.

Smoking Cessation. Patients with IHD should be counseled to make smoking cessation a priority. See the chapter on ▶ Tobacco Cessation for information on strategies and clinical interventions that may help patients become smoke free.

Symptom Control. Options for antianginal therapy include beta-blockers, nitrates, and calcium channel blockers. Beta-blockers are the first-line recommendation for control of angina [2]. By reducing myocardial oxygen demand, they reduce the frequency of chest pain episodes and improve exercise tolerance. In addition to their benefit for symptom 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.

Ranolazine is a newer therapy 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 add-on 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 [2]. Ranolazine can be used in patients with bradycardia or low blood pressure.

Other Recommendations. 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 [2]. Referring a patient to a dietitian may be reasonable.

Coronary Revascularization. When angina cannot be controlled with medical management, referral to a cardiologist for consideration of coronary angiography and potential revascularization is recommended.

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Cardiac Arrhythmias

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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 and rate of 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 emergency response. In stable patients, the workup focuses on identifying the arrhythmia, its cause, and its effect on cardiac function and on treating it to improve patients' symptoms and reduce morbidity and mortality.

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.

Figure 1 [1] shows a schematic 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 60–100 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).

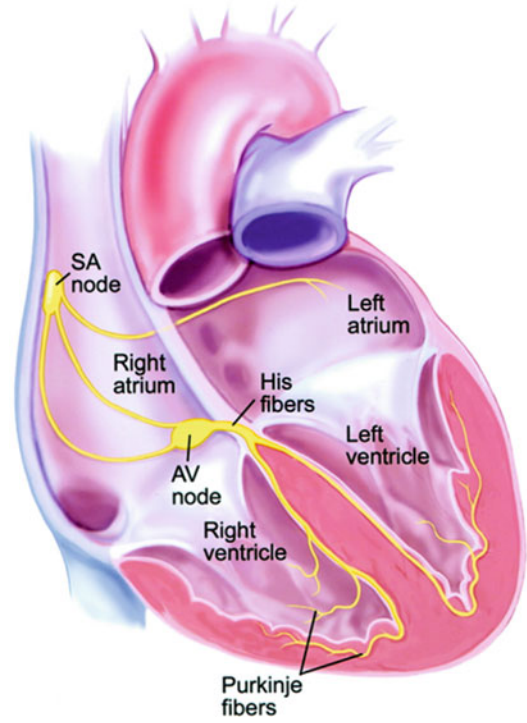

Fig. 1 Diagram of the heart and the electrical conduction system of the heart (From Ref. [1])

At the molecular level, the generation of the AP is due to unstable transmembrane potential caused by a slow sodium leak into the cells, depolarizing the membranes until the threshold is reached that triggers an AP. Cardiac cells have several voltage-gated ion channels, and the in and out flow of 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 but do not participate in the generation or transmission of electrical activity; they modulate cardiac function.

Three main mechanisms have been identified as the causes of arrhythmias: increased automaticity, triggered activity, and reentry. Reentry 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, 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 noncardiac 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 physical exam (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	Noncardiac
CAD: myocardial ischemia or infarction	Pulmonary disease
Heart failure	COPD, PE, pneumonia
Structural heart disease: congenital or acquired	Cor pulmonale
Dilated cardiomyopathy	Thyroid disease
Ventricular hypertrophy	Drug toxicity
Valvular disease	Antiarrhythmics
Atrial septal defect	Beta agonist inhalers
Ebstein anomaly	Lithium
Epicardial, myocardial, and endocardial diseases: infectious, injury, or drug toxicity	Drugs that increase QT interval
	Electrolyte abnormalities
Iatrogenic	Recreational drugs
Post-cardiac catheterization	Diet pills
Post-cardiac surgery	Collagen vascular disease
Post ablation	Infiltrative disease
Post-ICD placement	Hypothermia

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 complete metabolic panel, magnesium, phosphate, 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 Arrhythmias

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 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, short fasting, etc.

Electrical cardioversion is accomplished by delivering a direct current electric shock of 50–360 J 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.

Pharmacologic cardioversion and maintenance of NSR have been challenging due to limited long-term efficacy of drugs, the risk of triggering ventricular arrhythmias, and their long-term adverse side effects [3]. 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 (Tikosyn), 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. Drugs are classified according to their mode of action, although some drugs have more than one effect [9–12]. Table 2 shows drug classification, indications, and contraindications, potential adverse side effects, and their pharmacokinetics. Detailed description of each drug and its pharmacology is beyond the scope of this chapter.

Class I. These drugs block Na channels and therefore act on the depolarization phase of the cardiac AP. They are further subdivided into three subclasses according to their effect on the

Table 2 Antiarrhythmic drugs

Class		Medication Name and MOA	Indications	Contraindications	Side effects (SE)	Half-life and pharmacokinetics
I OR Sodium Channel Blockers	Ia	Quinidine (Qualaquin) different types: Gluconate, sulfate ↓↓ Phase 0 slope	A-Fib, A- flut, VT	HtoD, myasthenia gravis, Immune thrombocytopenia, thrombocytopenic purpura, Digitalis toxicity, complete AV dissociation	QT prolongation, paradoxical pulse in A-Fib/A-flut, bradycardia in SSS, ↓ BP, diarrhea, vertigo, vision changes Warnings: HB without pacemaker Pregnancy risk C Lactation risk L2	6–8 h
		Procainamide[a] ↑ AP duration	VT	HtoD, complete HB, 2nd- or 3rd-degree AVB SLE, torsades de pointes	↓ BP, widened QRS, rash, agranulocytosis, drug-induced lupus Warnings: complete HB, SLE, torsades de pointes Monitor *N*-acetylprocainamide (NAPA) levels Pregnancy risk C Lactation risk L3	3–4 h E: renal Adjust dose if CrCl < 50 ml/ min
		Disopyramide (Norpace) ↑ Effective refractory period	VT	HtoD, cardiogenic shock, congenital prolonged QT, 2nd- or 3rd-degree block	↓ BP, HF, widened QRS, QT prolongation; 1st HB (reduce dose), anticholinergic effects Warnings: 1st- and 2nd-degree HB Pregnancy risk C Lactation risk L2	7–8 h E: renal Adjust dose if CrCl < 40 ml/ min
	Ib	Mexiletine[a] ↓ AP duration	VT	HtoD, cardiogenic shock, 2nd- and 3rd-degree AVB, if no pacemaker is present	Acute liver injury, leukopenia, agranulocytosis, tremor, blurry vision, lethargy, and nausea Warnings: SSS, HB, ↓ BP, HF Pregnancy risk C Lactation risk L2	10–12 h
		Phenytoin (Phenytek, Dilantin) (Rarely used in arrhythmia) ↓ Effective refractory period	VT secondary to digoxin	HtoD or other hydantoins, concomitant use with delavirdine or rilpivirine	Rash, gingival swelling, constipation, N/V, ataxia, slurred speech, SLE, SJS, agranulocytosis, pancytopenia, hepatotoxicity, suicidal thoughts, drug withdrawal seizure	14–22 h E: mostly Liver
		Lidocaine (Xylocaine) ↓ Phase 0 slope	VF, VT	HtoD or to local anesthetics of the amide type	↓ HR, HB, cardiovascular collapse, agitation, anxiety, coma Pregnancy risk B Lactation risk L2	1–2 h E: renal

(*continued*)

Table 2 (continued)

Class		Medication Name and MOA	Indications	Contraindications	Side effects (SE)	Half-life and pharmacokinetics
		Tocainide (Tonocard)	VF, VT	HtoD, 2nd- and 3rd-degree AVB, HF, ↓K, liver and kidney disease	↓ HR, ↓ BP, rash, abdominal pain, ataxia, tremor, vertigo, blurry vision	12 h
	1c	Flecainide (Tambocor) ↓↓↓ Phase 0 slope	PAF, ventricular arrhythmia, PSVT, P-atrial flut	HtoD, RBBB with left hemiblock without pacemaker, 2nd- and 3rd-degree AVB without pacemaker	Palpitation, dyspnea, headache, dizziness, fatigue. Cardiogenic shock, VF, VT, torsades de pointes	20 h prolonged HL in renal impairment
		Propafenone (Rythmol) ↔ AP duration	PSVT and PAF Without Structural Heart disease, VT	HtoD, bradycardia, Brugada syndrome, severe bronchospasm, COPD, cardiogenic shock, HF, electrolyte imbalance, marked hypotension. SSS and AVB without pacemaker	New or worsen arrhythmias, worsen HF, dose-related ↑ in PR, QRS intervals, HB, neutropenia, and/or agranulocytosis. Warnings: bradycardia, shock, prolonged QT interval, CAD Pregnancy risk C Lactation risk L2	5–7 h E: liver Dose adjust with severe liver and kidney disease
ll Beta blockers Most commonly used	B1S: metoprolol (Toprol), atenolol (Tenormin). Esmolol (Brevibloc) Nβ1S: Coreg (carvedilol), Sotalol (Betapace, Sorine, Sotylize) Propranolol (Inderal, Innopran, Hemangeol) ↓SA node automaticity ↓ HR and conduction ↓ chronotropy and inotropy by inhibition of β1 receptor		VT, PVC, VF ST, A-Fib, A-flut, PAT	HtoD, ↓ BP or shock, severe bradycardia, HB >1st degree (unless pacemaker), MI precipitated by cocaine, overt HF with pulmonary edema (start at low dose)	↓ BP, ↓ HR, 1st-degree HB, dizziness, fatigue, rash, diarrhea, dyspnea, bronchospasm, hypoglycemia, seizure	Met: IV 3–4 h PO:7–9 h Aten: 6–9 h Prop: 3–6 h Esm: 9 min Sot: 12 h Carv: 7–10 h

lll K channel blockers	Ibutilide (Corvert)	A-Fib, A-flut	HtoD, HF, prolong QT, ↓ HR, MI, electrolyte abnormalities, liver disease. Not to use with Class 1 or other Class III	↓ HR, HB, prolong QT, VA. Torsades de pointes, CVA, renal failure, pulmonary edema	6 h
	Amiodarone (Pacerone, Cordarone, Nexterone) Delays repolarization (phase III)	Supraventricular arrhythmia, VA	HtoD, severe bradycardia, syncope without pacemaker, severe sinus node dysfunction, 2nd- and 3rd-degree AV blocks (unless with pacemaker). Cardiogenic shock	↓ HR, ↓BP, photodermatitis, optic neuritis, thyroid dysfunction, liver failure, abnormal gait and coordination, anaphylaxis, pseudotumor cerebri, ARDS	Weeks
	Dofetilide (Tikosyn) Prolongs AP phase III	A-Fib, A-flut	HtoD, prolong QT, severe renal impairment, concomitant use of cimetidine, hydrochlorothiazide, ketoconazole, prochlorperazine, verapamil	Prolong QT, VF, torsades de pointes, CP, dizziness, headache	10 h
IV Ca channel blocker	Verapamil (Calan, Covera, Isoptin, Verelan) Diltiazem (Cardizem, Cartia, Dilacor, Dilt-CD, Diltzac, Taztia, Tiazac, Matzim) Block L-type Ca channels Most effective at SA and AVN ↓ HR and conduction	A-Fib, A-flut with RVR	HtoD. Ver: A-Fib, A-flut associated with WPW syndrome. SSS, 2nd- and 3rd-degree AVB without pacemaker, HF with EF < 30% hypotension HtoD. Dilt: all of the above Newborns, acute MI with pulmonary congestion, administration within a few hours of IV β blockers	↓ HR, HB, worsening of HF, ↓BP Warnings: WPW, SSS, HB, other AV nodal blockers Pregnancy risk C Lactation risk L2	Ver: 7 h Dilt: 4–8 h E: liver for both

(*continued*)

Table 2 (continued)

Class	Medication Name and MOA	Indications	Contraindications	Side effects (SE)	Half-life and pharmacokinetics
Miscellaneous	Digoxin (Lanoxin, Lanoxicaps, Digox, Digitek) Inhibits Ca-K ATPase, causing ↑ chronotropic and ↓ inotropic effects	A-Fib, A-flut with RVR, HF	HtoD, VF	Arrhythmias, N/V Warnings: bradycardia, HB, renal Failure, hypokalemia Pregnancy risk C Lactation risk L2	30 h Narrow therapeutic range E: renal
	Adenosine (Adenocard, Adenoscan) ↓ AV node conduction Velocity, ↑ refractory period	PSVT	HtoD, asthma, 2nd and 3rd AVB, symptomatic bradycardia, and SSS without a pacer	AVB, flushing, chest burning due to bronchospasm, brief period of asystole Warnings: HB, wide complex VT Pregnancy risk C Lactation risk probably safe	<10 s
	Dronedarone (Multaq) Combined effects of Classes I–IV	A-Fib or A-flut	HtoD. SSS, 2nd and 3rd AVB without pacemaker, liver, and lung toxicity. HF (New York Class lV or recent decompensation), severe liver impairment and use of CYP3A inhibitors. Prolonged QT > 500 and PR interval > 280 s	Stop Class I or III agents first. HF, HB, bradycardia, QT prolongation Pregnancy risk X Lactation risk unknown	13–19 h

Data presented in this table are from Refs. [9–12]

Note: The reader is responsible for verifying applicability according to patient's condition, age, liver/kidney functions, and comorbid conditions

A-Fib atrial fibrillation, *A-flut* atrial flutter, *AP* action potential, *APD* action potential duration, *ARDS* acute respiratory distress syndrome, *Aten* atenolol, *AV* atrioventricular, *AVB* atrioventricular block, *BP* blood pressure, *β1S* β 1 selective, *CAD* coronary artery disease, *Carv* carvedilol, *COPD* chronic obstructive pulmonary disease, *CrCl* creatinine clearance, *CVA* cerebral vascular accident, *Dilt* diltiazem, *E* elimination, *Esm* esmolol, *HB* heart block, *HF* heart failure, *Hep* hepatic, *HL* half-life, *h* hours, *HR* heart rate, *HTN* hypertension, *HtoD* hypersensitivity to drug or its components, *LV* left ventricular, *Met* metoprolol, *MI* myocardial infarction, *MOA* mechanism of action, *Nβ1S* non-β1 selective, *N/V* nausea and vomiting, *PAF* paroxysmal atrial fibrillation, *PAT* paroxysmal atrial tachycardia, *Prop* propranolol, *PSVT* paroxysmal supraventricular tachycardia, *PVC* premature ventricular contraction, *RBBB* right bundle branch block, *Ren* renal, *sec* second, *SJS* Stevens-Johnson syndrome, *SLE* systemic lupus erythematosus, *Sot* sotalol, *SSS* sick sinus syndrome, *ST* sinus tachycardia, *VA* ventricular arrhythmias, *Ver* verapamil, *VF* ventricular fibrillation, *VT* ventricular tachycardia, *WPW* Wolff-Parkinson-White

Pregnancy risk category C = animal studies have shown an adverse effect on the fetus, but the risk of medication is not known in human

Lactation risk L2 (probably compatible) = studied in a limited number of women without findings of increased risk of adverse effects in the infant

[a]Medications without brand names in the USA

duration of the AP: shortening it, Class Ia; lengthening it, Class Ib; or no effect, Class Ic.
- Class Ia agents prolong the initial phase of the AP thus delaying depolarization. They also increase the absolute refractory period. They include quinidine (Qualaquin), procainamide, and disopyramide (Norpace).
- Class Ib. These drugs shorten the duration of the AP by increasing repolarization. They include lidocaine (Xylocaine), phenytoin (Phenytek, Dilantin), mexiletine, and tocainide (Tonocard).
- 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. They include encainide, flecainide, propafenone, moricizine.

Class II. These are β blockers which have antisympathetic activity by blocking β1 adrenergic receptors, slowing HR by delaying conduction at the AV node [11]. Among them are propranolol (Hemangeol, Inderal, InnoPran), esmolol (Brevibloc), timolol, metoprolol (Toprol), atenolol (Tenormin), and bisoprolol (Zebeta).

Class III. These drugs block K channels and prolong repolarization and thus the refractory period of cardiocytes. They are useful in treating reentry arrhythmias. Among them are amiodarone, sotalol (Betapace, Sorine, Sotylize), ibutilide, dofetilide, and dronedarone (Multaq).

Class IV. They are calcium channel blockers (nondihydropyridine) that delay conduction at the AV node, slowing HR. They also inhibit heart contractility and thus are contraindicated in patients with heart failure. They include diltiazem (Cardizem, Cartia, Dilacor, Dilt-CD, Diltia-CD, Taztia, Tiazac, Diltzac, Matzim) and verapamil (Calan, Covera-HS, Isoptin SR, Verelan).

Class V, Miscellaneous. This class includes drugs with different effects from the above classes. They include digoxin (Lanoxin, Lanoxicaps, Digitek, Digox), adenosine, and magnesium
- Digoxin decreases conduction at the AV node, and it increases vagal activity. Its main indication today is in addition to β blockers and calcium channel blockers to slow HR in AF.
- Adenosine (Adenocard, Adenoscan), a purine nucleoside with a half-life of <30 s, transiently blocks the AV node, and it is useful in stopping SVT due to reentry circuits within the AVN, atria, and accessory AV circuits. When used, patients need to be under continuous cardiac monitoring, be warned about transient unpleasant side effects (flushing, metallic taste, lightheadedness, and diaphoresis, lasting <1 min), and resuscitation equipment must be available. Adenosine is as effective as CCB in terminating SVT [13]. It is contraindicated in wide QRS tachycardias, 2nd and 3rd degree AVB without a pacer, sick sinus syndrome without a pacer, decompensated heart failure, hypotension, heart transplant patients, and severe asthma.
- Magnesium sulfate is only effective in the treatment of torsades de points, a deadly form of ventricular fibrillation.

Ablation Therapy

Electrophysiology studies are used to identify, study, and accurately map the foci of arrhythmia. Ablation therapy is then used to destroy abnormal foci and pathways by delivering radiofrequency energy to the target site(s). The injury to heart tissue is thermal and creates scarring, inflammation, and then necrosis. Sometimes the same arrhythmia recurs within days, weeks, or months, and the procedure may need to be repeated. Indications for ablation therapy include AF, WPW syndrome, and preexcitation [4, 6–8].

Pacemakers and Defibrillators

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. 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. Detailed pacemaker settings and function are beyond the scope of this chapter. Several studies have demonstrated their effectiveness in preventing sudden death from arrhythmias [4–6].

The ACC/AHA and the North American Society of Pacing and Electrophysiology recommend the implantation of pacemakers in patients with complete 3rd degree AV block, advanced 2nd degree AVB (block of two or more consecutive P waves), symptomatic Mobitz I or Mobitz II 2nd degree AV block, Mobitz II 2nd degree AV block with a widened QRS or chronic bi-fascicular block, and exercise-induced 2nd or 3rd degree AV block (in the absence of myocardial ischemia). They also recommend biventricular pacing for patients with dilated cardiomyopathy (ischemic and nonischemic), those with an LVEF $<35\%$, those with QRS complexes >0.12 ms, and in patients with New York Heart Failure Class III or IV heart failure, despite optimal medical treatment [4–7].

Patients with implanted pacemakers need to be monitored regularly by cardiology for proper function, programming, and battery life and to monitor patient's clinical symptoms.

Defibrillators deliver unsynchronized electrical shocks to the heart with the aim to stop a lethal arrhythmia and reestablish a viable cardiac rhythm. 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. 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 surgical disruption of abnormal conduction pathways within the atria, known as Maze procedure, and the obliteration the left atrial appendage (LAA).

In the Maze procedure, incisions are made in the atria to isolate and interrupt reentry circuits while maintaining the physiologic activation of the atria. In another version, incisions are made to create an electrical corridor from the SA to the AV node. The Maze procedure has undergone multiple revisions since its development, and it is considered for patients who need invasive cardiac surgery for other reasons [14].

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 [15, 16]. It is only recommended for patients undergoing other cardiac surgery, most commonly mitral valve repair [3, 4].

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 Tachyarryhthmias (SVT)

These arrhythmias originate above the ventricles and involve the atria or the AV node for initiation and propagation. These arrhythmias are due to reentry circuits or accessory pathways, most commonly the AV nodal reentrant tachycardia, the atrioventricular reentrant 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.

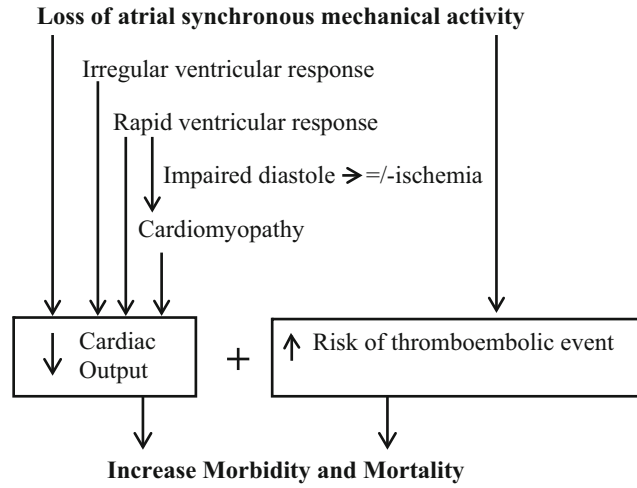

Fig. 2 Clinical implications of atrial fibrillation

Key questions to answer in evaluating SVT are: 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 the heart rate and mechanical function? [17].

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 [18, 19]. It worsens heart failure and increases mortality in the setting of myocardial infarct [20, 21]. It causes about 10 % of strokes, and these are more devastating and a major cause of disability. Figure 2 shows the deleterious effect of AF [22].

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 reentry 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. AF due to noncardiac 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) 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 complex 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 infarction, emergency evaluation and treatment are 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

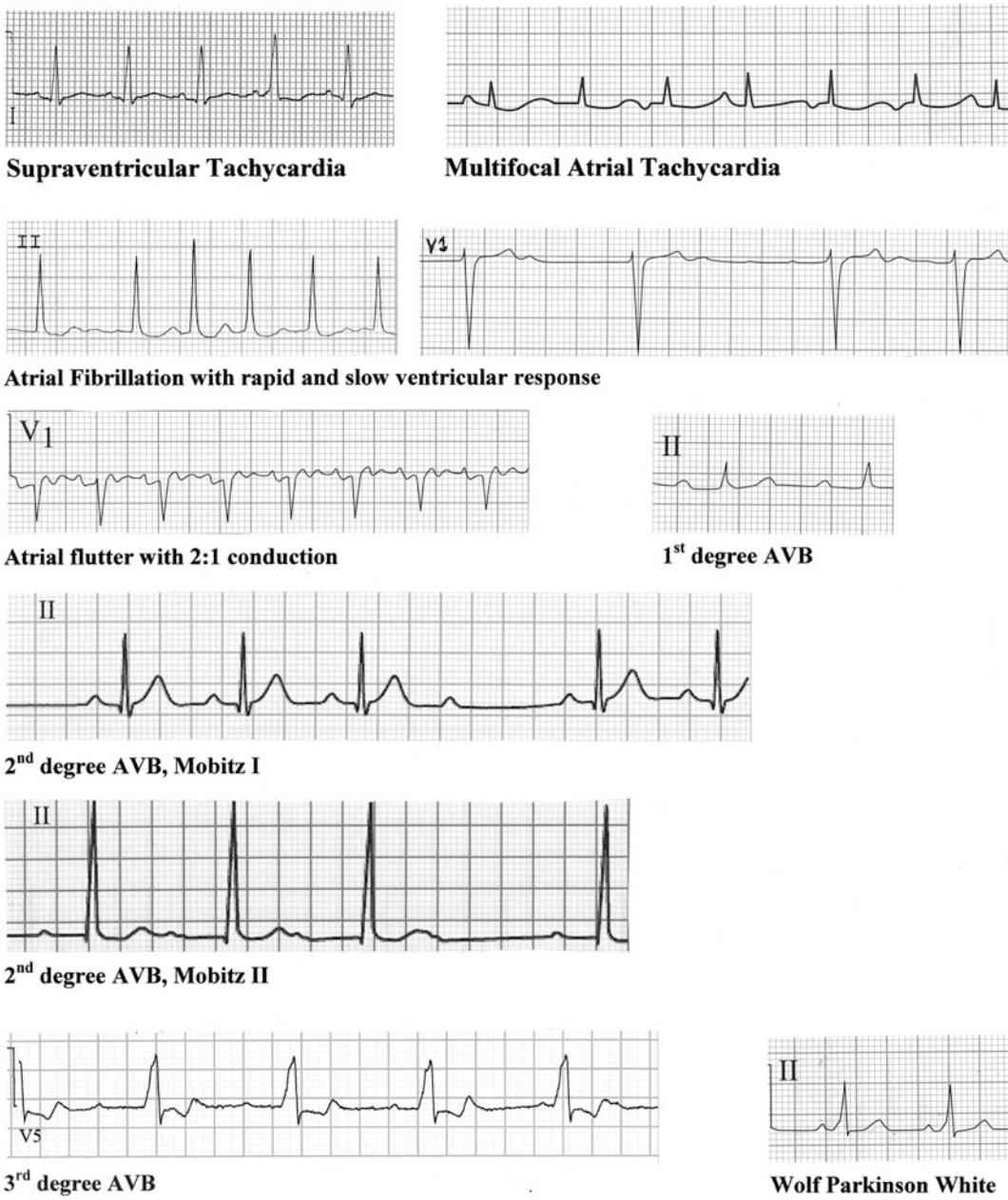

Fig. 3 Most common supraventricular arrhythmias. For each arrhythmia, see discussion in corresponding section

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 of pre- and 3–4 weeks post-anticoagulation. Pharmacologic cardioversion with antiarrhythmic drugs has limited efficacy. Commonly used drugs include flecainide, propafenone, dofetilide, amiodarone, dronedarone, and sotalol. 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.

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/ LV dysfunction	1	0	0	No
Hypertension	1	1	1.3	
Age <65 65–75 >75	0 1 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 For patients unable or who refuse above choices Aspirin 81–325 mg qd Clopidogrel 75 md qd
Diabetes	1	3	3.2	
Stroke/TIA Thromboembolism	2	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

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, at the cristae terminalis, and coronary sinus [23]. The ACCF/AHA/HRS AF guidelines recommend it for patients with recurrent AF who are symptomatic but who have no structural heart disease [3].

Most patients are treated with ventricular rate control vs rhythm control [24, 25]. 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 nondihydropyridine 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 [26]. 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 [14–16].

Anticoagulation significantly reduces the risk of stroke. Several stratification tools to assess both the risk of stroke and risk of bleeding have been developed. Although they have limitations, they are useful in evaluating patients' risks and benefits for long-term anticoagulation.

The widely used CHADS2 acronym score, a validated tool to assess risk of stroke, has been replaced by CHAD2DS2-VASc [27]. Table 3 shows the current risk stratification and recommendations for anticoagulation [3]. Similarly, several tools have been developed to assess the risk of bleeding from anticoagulation. The ATRIA and now preferred HAS-BLED tools are used to assess risk of bleeding [28–31]. Risk factors include anemia, severe renal disease, age, previous bleeding, hypertension, liver disease, labile INR, and drug or alcohol use.

Warfarin (Coumadin, Jantoven) has been the corner stone of anticoagulation, but its use is challenging due to its narrow therapeutic range,

Table 4 Pharmacological properties of approved anticoagulants available for the prevention of thromboembolism in atrial fibrillation

Property mechanism	Warfarin Vitamin K antagonist	Dabigatran Direct thrombin inhibitor	Rivaroxaban Factor Xa inhibitor	Apixaban Factor Xa inhibitor
Dosing	Variable (dose adjusted on the basis of international normalized ratio)	150, 110 mg bid 75 mg bid for creatinine clearance ± 15–30 (USA only) Not recommended if < 15	20 mg daily;15 mg daily for creatinine clearance 15–50, Not recommended if <15	5 mg bid; 2.5 mg bid for patients with > 2 of the following: Creatinine > 133 μm/L, age > 80 years or weight < 60 kg, creatinine clearance± <15: no data available
Oral bioavailability	100 %	3–7 %	60 %	58 %
Time to effect (h)	72–96	1–2	2–4	3–4
Half-life (h)	40	12–17	5–9	8–15
Notable drug numerous interactions		Strong P-glycoprotein inducers		
		Strong P-glycoprotein inhibitors with concomitant kidney dysfunction	Strong P-glycoprotein inhibitors, strong cytochrome P450 inducers and inhibitors	

From Ref. [38]

multiple drug and food interactions, and need for frequent monitoring. The therapeutic goal is an INR between 2 and 3 for patients 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 % [32–35].

Newer anticoagulants such as direct thrombin inhibitors and factor Xa inhibitors have emerged. As new data is gathered on their effectiveness and safety and their costs decrease, they likely will change anticoagulation practices.

Dabigatran (Pradaxa), a thrombin inhibitor, is as effective as warfarin in preventing stroke and systemic emboli. Rates of major bleeding were similar to those of warfarin, except for fewer intracranial bleeds but increased gastrointestinal bleeds. Caution and adjustment in dosing is needed for patients with kidney disease [36].

Factor Xa inhibitors now available are rivaroxaban (Xarelto), apixaban (Eliquis), and edoxaban (Savaysa). As compared to warfarin, rivaroxaban and edoxaban were non-inferior in preventing stroke and systemic thromboembolic events and have the same effect on major and non-major bleeding. Apixaban is superior to warfarin in stroke prevention and has the same bleeding rate as warfarin. Doses need to be adjusted for patient with kidney disease [37, 38].

The main advantages of thrombin and factor Xa inhibitors over warfarin include fixed dosing, no food interactions, fewer drug interactions, and no need for monitoring. Their major drawbacks are high cost, difficulty in reversing their effect in emergency situations, and not FDA approved (as of 2014) for valvular AF, pregnant or lactating patients, and those with advanced kidney disease. Table 4 shows a summary of approved anticoagulants available and their characteristics [37, 38].

Atrial Flutter

Atrial flutter is an organized regular rhythm caused by a reentry circuit around the tricuspid

valve. It is often seen after cardiac surgery or cardiac ablation. AF and atrial flutter can occur 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 is 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. Class Ic drugs have not been effective and may be dangerous due to their pro-arrhythmic effects. 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.

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 preexcitation (Fig. 3). Drugs with AV node suppression effect such as BB, CCB, digoxin, and adenosine are contraindicated. Propafenone, flecainide, sotalol, or amiodarone can be used, but most patients need EPS to identify the accessory pathways and undergo ablation.

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, 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 where the lesion is. The severity is described in degrees.

In 1st-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, nondihydropyridine CCB, and beta blockers can be the culprit.

There are two types of 2nd-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 patterns appear. In patients with bi-fascicular block, a pacemaker is recommended.

In 3rd-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. Patients with asymptomatic bradycardia do not need treatment but need close follow-up.

Ventricular Arrhythmias (VAs)

VAs are caused by electrical activation of ventricular cardiac cells without atrial or nodal influences, most commonly triggered by reentry 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. VAs are classified according to their frequency, persistence, and effect on ventricular contraction.

Premature Ventricular Contractions (PVCs)

PVCs (Fig. 4) are very common in the general population. Isolated events in patients with healthy hearts do not require treatment. First-line therapy for symptomatic patients is either a β blocker or nondihydropyridine CCB. Some patients may benefit from EPS and catheter ablation if specific foci are identified. PVCs also present in bigeminy, trigeminy, or quadrigeminy patterns when followed by 1, 2, or 3 normal beats, respectively (Fig. 4). Their clinical significance depends on their frequency, complexity, and 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 [39]. 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 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.

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, and 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

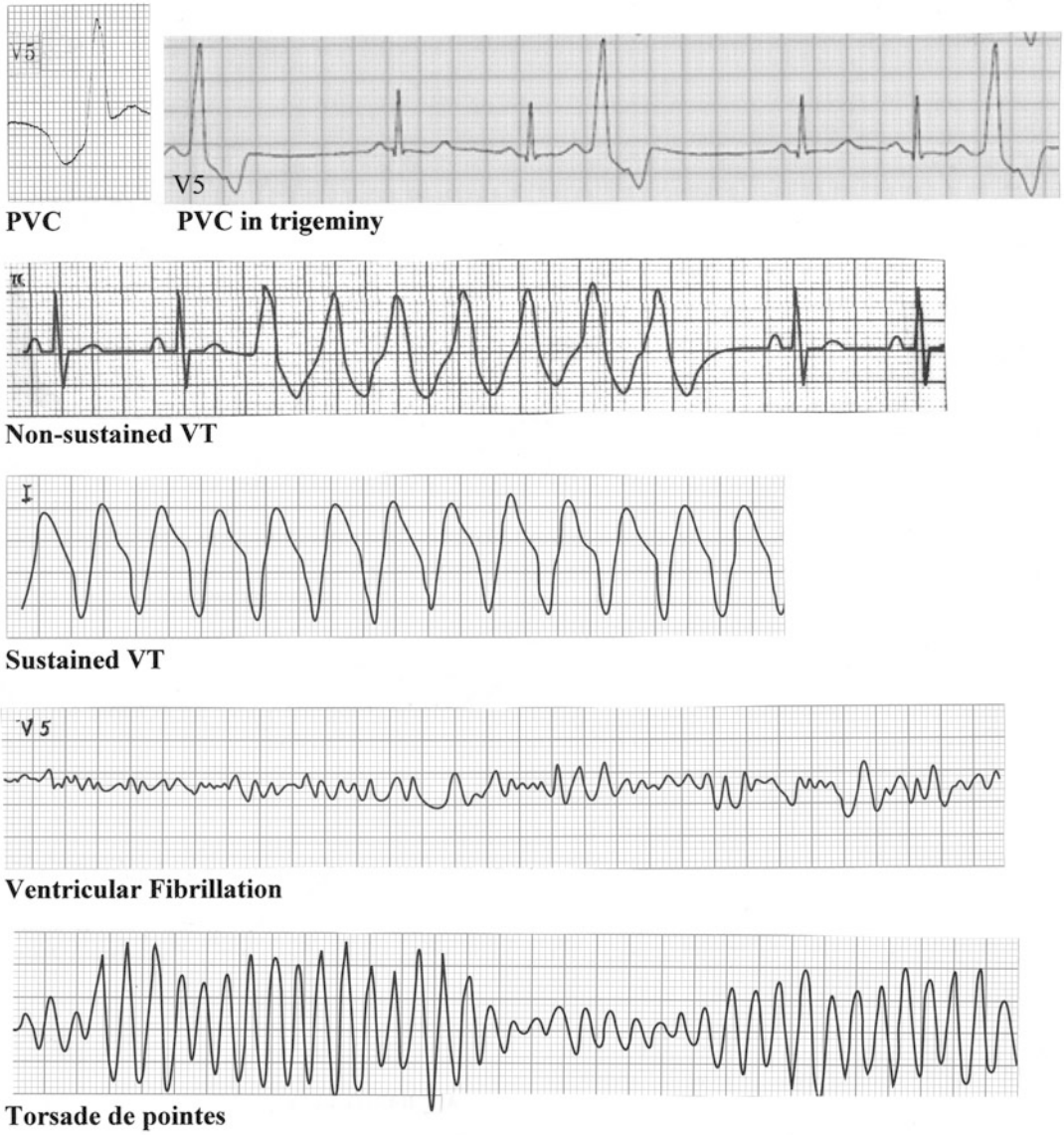

Fig. 4 Most common ventricular arrhythmias. For each arrhythmia, see discussion in corresponding section

MI and in HF. Patients with syncope should have EPS and ablation therapy if indicated.

Ventricular Fibrillation (VF)

This deadly arrhythmia is 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.

Torsades de Pointes

It is a rare form of VT characterized by repeated cycles of QRS complex changing in amplitude 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 [40, 41]. This has been the reason to install automatic external defibrillators (AED) in public places.

In 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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Contents

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Introduction

The challenge of valvular disease is in distinguishing the benign nonprogressive disorder from a concerning and potentially dangerous structural disease [1, 2]. 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 [3, 4]. 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 [5].

The Third Heart Sound

The third heart sound S3 occurs after S2; it has a low frequency as such and may be the most difficult heart sound to hear. It has age-dependent indications. In patients under 30 years old, it can be physiologic and not associated with abnormal structure or function. It may be suspicious in patients 30–40 years of age. These patients may have conditions such as thyrotoxicosis, pregnancy, or anemia, which may produce the third heart sound without the presence of heart pathology. An S3 should be considered an indication of pathology in patients 40 or older. In this age group, the S3 often correlates with dysfunction or volume overload in the ventricles [4, 5]. Pathology that leads to the S3 includes ventricular overload such as high output state (pregnancy, thyrotoxicosis, and anemia), valvular regurgitations, or excessive fluid overload. Extensive periods of this diastolic overload may lead to permanent and irreversible ventricular dysfunction.

The Fourth Heart Sound

The fourth heart sound is of low frequency and occurs just prior to S1. The S4 is produced as a result of decreased compliance within the ventricles. As such, the presence of an S4 typically indicates hypertrophy of the ventricles due to pathology such as long-term hypertension, hypertrophic cardiomyopathy, or aortic stenosis. The fourth heart sound is most prominent at the apex and may also be palpable. Although there is some disagreement in whether or not S4 may be heard in the absence of disease, the presence of a clearly audible and palpable S4 has high correlation with pathology. On hearing an S4, reasons for the decreased compliance should be pursued and when possible mitigated or corrected [3–5].

Innocent and Physiologic Murmurs

Heart murmurs are the result of turbulent flow through the structures of the heart. The vast majority of murmurs heard in primary care in children and up to 40 % in adults are innocent or physiological murmurs, meaning no correlation with heart pathology. Innocent murmurs have no cardiac pathology, and physiologic murmurs result from the alteration of flow due to perturbations of physiology, examples being whether in a normal state such as pregnancy or abnormal such as thyrotoxicosis and anemia [3–5].

Characteristics

Murmurs are characterized by their timing in the heart cycle, their auditory volume as noted by their grade (Table 1), and their location and response to maneuvers. Innocent murmurs are always either systolic or continuous and never solely diastolic. Diastolic murmurs are always pathologic until proven otherwise and would likely need referral for further evaluation. Innocent murmurs are generally soft and never greater than grade 3, usually having no radiation [1, 2, 5].

Physical Maneuvers

Exam room maneuvers may alter the qualities of a murmur and may help to define and diagnose innocent versus pathological. 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 [3, 5].

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. 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 [5].

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 or mitral valve prolapse decrease in volume [5].

Valvular Heart Disease

Prevalence

The overall incidence of heart murmurs would be impossible to determine as their presence due to innocent and physiologic etiologies can and does change over a patient's life span. Although most cases of valvular heart disease are chronic, many are often asymptomatic; the prevalence of structural changes due to actual valvular heart disease may be easier to delineate. Population-based studies using echocardiography have estimated the prevalence. One study which had well over 11,000 subjects each undergoing an echocardiograph determined a prevalence of about 2.5 %, and although there was no gender difference, this prevalence of disease increases with age >65. A prevalence of <2 % was noted before the age of 65 and an increase to 13.2 % after the age of 75 [1]. The overall etiology of acquired valvular heart disease has changed significantly in the last 50 years due to a sequela of antibiotics and the subsequent decrease in rheumatic fever-related valvular disorders [5, 6].

Table 1 Grade of murmurs

Grade	Characteristics of murmurs
1	Audible under optimal conditions by an expert
2	Easy to hear with stethoscope but soft
3	Moderately loud, no thrill
4	Very loud with a palpable thrill, with stethoscope on chest
5	Audible with stethoscope partly off chest with a thrill
6	Audible without a stethoscope with a thrill

Aortic Stenosis

Etiology

Aortic stenosis has congenital, rheumatic, and degenerative causes, all contributing to increased calcification of the aortic valve and its subsequent eventually problematic stenosis [4, 6]. The aortic valve that is congenitally bicuspid has a greater tendency to calcify and is more vulnerable to infective endocarditis. Rheumatic disease is in decline in developed countries due to the prevalence of antibiotic treatment, but rheumatic aortic stenosis when present is the result of cusp fusion and calcification many years after the episode of rheumatic fever. Degenerative or senile aortic stenosis is an increasingly problematic finding in the elderly. Risk factors for aortic stenosis are similar to those of coronary artery disease and atherosclerotic disease [1, 7].

Symptoms

Initially, aortic stenosis is asymptomatic, and as the stenosis slowly progresses, symptoms become more severe. Symptomatic individuals have

variable presentations with severe stenosis, which may demonstrate syncope, anginal symptoms, and/or heart failure. Patients with signs or symptoms of aortic stenosis need a transthoracic echocardiogram to evaluate the cause of the stenosis, any hemodynamic changes, and left ventricular size and function [4, 5, 8]. Symptomatic stenosis must be addressed, and with the onset of symptoms, the average survival drops to 3 years.

Physical Findings

Incidental asymptomatic murmurs found in elderly patients must differentiate the benign aortic sclerotic valve from the potentially asymptomatic and less common aortic stenosis [1]. Aortic stenosis may be indicated by the presence of a systolic ejection murmur best heard over the aortic area and radiating to one or both carotids. There may be an accompanying early diastolic murmur if there is a coexisting aortic regurgitation present [5].

Natural History and Complications

Degenerative aortic stenosis progresses slowly during its asymptomatic latent period. Once symptomatic morbidity and mortality increase significantly, there may be anginal symptoms even with clean coronaries, debilitating syncope, and progressive heart failure. A 2014 study of patients with severe aortic stenosis undergoing noncardiac surgeries found that they had increased major adverse cardiovascular events mainly due to heart failure, but no difference in postoperative 30-day mortality, but severe aortic stenosis in this study of postoperative patients was the strongest predictor of mortality at 1 year [3, 4, 9].

Medical Therapy

Medical therapy is based on the presence of concomitant coronary artery disease and/or left ventricular dysfunction. For patients with severe aortic stenosis and systolic failure, surgical valve replacement is recommended. However, if medical therapy is chosen, optimizing medical management of left ventricular dysfunction is managed with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) with beta-adrenergic blocking agents. There must be caution regarding rapid blood pressure decreases in patients with stenotic lesions [4].

Timing of Surgery

Once a patient with aortic stenosis becomes symptomatic, whether syncope, angina, or heart failure, the benefits of valve replacement surgery often greatly outweigh the risks. In a patient symptomatic with aortic stenosis, a cardiology consultation is recommended for discussion regarding possible surgical interventions versus transcatheter aortic valve replacement. Surgery may also be considered in asymptomatic patients with severe aortic stenosis and one of the following: a calcified aortic valve, an exercise test demonstrating decreased tolerance or a fall in blood pressure during the exercise, or undergoing another cardiac surgery [4].

Aortic Regurgitation

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. Aortic regurgitation may present with tachycardia, cardiogenic shock, and pulmonary edema and is a surgical emergency. Acute aortic regurgitation derives from a rapid change in the aortic valve causing an acute abnormality, which may arise from etiologies 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 [3–5].

Chronic Aortic Regurgitation

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 [3–5].

Etiology

Aortic regurgitation has age-related etiologies. In patients younger than 50 years of age, the predominant etiologies include infectious endocarditis, Marfan's syndrome, syphilis, post-inflammatory changes, and rheumatic heart disease. For age >50 years, etiologies include bicuspid aortic valve and calcific valvular disease [4, 7].

Symptoms and Physical Findings

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 [1, 6, 8].

Aortic regurgitation is a diastolic murmur best heard at the left sternal border but may be associated with multiple other cardiac sounds and clinical signs. These signs may include the following:

An Austin Flint murmur characterized by the mid-diastolic murmur best heard at the apex.

The larger stroke volume may cause an aortic systolic flow murmur.

Traube's sign may present with a "pistol-shot" sound heard at the femoral pulse.

The patient's head may move up and down with the heartbeat; this is de Musset's sign.

Other findings, such as Muller's sign, which is cardiac pulsations noted at the uvula [4, 5].

Natural History and Complications

Chronic aortic regurgitation is a progressive abnormality in which the retrograde flow of blood through the aortic valve leads to increased volume and pressure in the left ventricle leading to long-term compensatory remodeling and eventually decreased ejection fraction, systolic dysfunction, and subsequent left ventricular dilation. Likelihood of a full recovery even with an aortic valve replacement may be decreased once the disease has progressed to severe left ventricular dilation. Therefore monitoring both symptoms and echocardiography are crucial in decision making with chronic aortic regurgitation. Echocardiography in asymptomatic patients may monitor the progression of disease, every 3–5 years in mild severity, every 1–2 years in moderate severity, and every 6–12 months in severe aortic regurgitation [4, 5] (Chapter 9, Valve Disease).

Medical Therapy and Timing of Surgery

The assessment and recommendations of a cardiologist will be helpful in determining the course of treatment for each patient with chronic aortic regurgitation and should be considered based on the patient's overall comorbidities. The most effective treatment for patients who can tolerate cardiac surgery is an aortic valve replacement. Aortic valve replacement should be considered for symptomatic patients with severe aortic regurgitation regardless of left systolic ventricular function, and patients with asymptomatic chronic severe aortic regurgitation and left systolic ventricular dysfunction, or if they have severe aortic regurgitation and are having to undergo another cardiac surgery. In symptomatic patients whose other comorbidities may preclude surgeries, ACE inhibitors/ARB and beta-adrenergic blocking medication have been associated with improved survival [4, 5, 8].

Mitral Valve Regurgitation

Acute mitral valve regurgitation is the result of acute changes in the mitral valve leading to sudden cardiovascular abnormalities secondary to acute left ventricular volume overload. Patients may become hemodynamically unstable and have pulmonary congestion and dangerously low cardiac output. This presents as an acutely decompensated, hypoxemic patient in cardiogenic shock. Rapid diagnosis and early interventions

may be lifesaving. Acute mitral regurgitation is typically the sequela of spontaneous rupture of papillary muscle secondary to an inferior myocardial infarction or from leaflet perforation or chordal rupture secondary to infectious endocarditis. The murmur in the acute decompensation may be short lived because of the decreased pressure gradient between the left atrium and left ventricle; therefore, in suspected acute mitral valve regurgitation, an echocardiogram evaluating the presence and severity of mitral regurgitation is essential. If the valve is poorly visualized on a transthoracic view, a transesophageal approach should be considered. Vasodilation medical therapy with a nitroprusside or nicardipine drip may be helpful in patients whose blood pressures are able to tolerate the lowering of the systolic aortic pressure. Surgical intervention in a timely manner is considered the definitive treatment for acute mitral valve regurgitation [4, 5].

Chronic Mitral Regurgitation

Etiology

Patients with chronic mitral regurgitation may have either primary or secondary chronic mitral regurgitation. Primary chronic mitral regurgitation is due to an abnormality in one or more components of the structure of the mitral valve itself. The leading cause of chronic mitral regurgitation is mitral valve prolapse with the recurrent prolapse weakening the chordae and making them more vulnerable to rupture. Connective tissue diseases and rheumatic fever are also less common contributors to the presence of primary chronic mitral regurgitation. In secondary chronic mitral regurgitation, the mitral valve is a structurally normal but functionally incompetent due to left ventricular dysfunction from severe dilation of the left ventricle. This dilation may be the result of progressive left systolic ventricular dysfunction secondary to coronary artery disease or less common, idiopathic myocardial disease [5, 7, 8, 10].

Symptoms and Physical Findings

Chronic mitral regurgitation can present in its severe stages with symptoms of decreased exercise tolerance and exertional dyspnea. In later stages, all of the hallmarks of the heart in systolic failure may be present. Physical signs include a pansystolic murmur heard best at the apex and may radiate to the axilla, a systolic thrill at the apex, a very prominent apex beat, a left parasternal heave, and a high-pitched S3 [5].

Natural History and Complications

Chronic mitral valve regurgitation has increased preload and decreased afterload in the left ventricle because of the regurgitant valve allowing some of the stroke volume back into the left atrium. Initially the dilation of the left ventricle and left atrium provides a compensatory remodeling. This compensation may facilitate asymptomatic function for years. The progressive changes due to this persistent volume overload eventually lead to clinically significant left ventricular dysfunction. Monitoring symptoms and echocardiograms are the cornerstone of evaluation for both primary and secondary chronic mitral valve regurgitation. Echocardiograms in asymptomatic patients may monitor the progression of disease, every 3–5 years in mild severity, every 1–2 years in moderate severity, and every 6–12 months in severe aortic regurgitation [4, 5, 8, 11].

Medical Therapy and Timing of Surgery

Chronic mitral regurgitation has no medical management recommendations other than continuing those associated with the coronary artery disease and/or heart failure in that may be present. There are different recommendations for surgical interventions based on the etiology and level of symptoms. As primary chronic mitral regurgitation progresses and the left ventricular ejection fraction decreases, patients may benefit from surgery when they are symptomatic from these changes or they are undergoing another cardiac surgery. Due to the overall structural

changes of the heart, the evidence for beneficial outcomes with surgery for asymptomatic secondary chronic mitral regurgitation is less robust. Therefore, in secondary chronic mitral regurgitation, surgery is reserved for symptomatic severe regurgitation [4, 11].

Mitral Valve Prolapse

Etiology

Mitral valve prolapse is the backward movement of one or both of the leaflets of the mitral valve. It is the most prevalent single valvular abnormality, affecting 2–3 % of the general population, and as such mitral valve prolapse is also the leading cause of mild mitral regurgitation [5, 7, 12].

Symptoms

Mitral valve prolapse itself does not increase mortality, and most cases are asymptomatic except some patients may note palpitations. If palpitations are present, a Holter/event monitor may be indicated to further evaluate. Mitral valve prolapse can however lead to mitral regurgitation, and although most mitral regurgitation from mitral prolapse is mild to trace, in some patients, the sequela associated with chronic mitral regurgitation may be significant, leading to decreased exercise tolerance and exertional dyspnea [4, 5].

Physical Findings

The presence of a mid-systolic click associated with a late systolic murmur, which may be high pitched and heard greatest at the apex, may shift with standing and squatting moving closer to the first heart sound and closer to the second heart sound, respectively. As mitral valve prolapse may be associated with mitral regurgitation, an echocardiogram is reasonable to evaluate the presence of this murmur [5].

Natural History, Complications, Medical Therapy, and Timing of Surgery

For mitral prolapse, the most important prognostic indicator is the presence and severity of mitral regurgitation. The development of atrial fibrillation or heart failure as a result of these valvular anomalies is an indication to consider specialty consultation and possibly surgery [4].

Mitral Stenosis

Etiology

The prevalence of mitral stenosis is highly associated with the prevalence of rheumatic fever; as such it is uncommon in developed countries and more common in the developing world. In developed countries, the etiology is mostly degenerative and can be associated with calcium encroachment, e.g., secondary to dialysis [4, 13].

Symptoms

Decreased exercise tolerance, shortness of breath, and exertional dyspnea are the most common presentation of mitral valve stenosis. The symptoms are the result of reduced flow through the valve and as such tend to increase as the mitral valve area decreases. Symptomatic patients with mitral stenosis should be considered for referral to discuss definitive treatment and possible surgical interventions [4, 5, 13].

Physical Findings

Physical findings of mitral stenosis are noted most during the presence of increased physical stress such as in times of exercise, infection, and rapid ventricular response. These physical findings may include a loud first heart sound, an opening snap, and a late diastolic murmur [5].

Table 2 Antibiotics for infective endocarditis prophylaxis for dental procedures

Antibiotic		
Single dose 30–60 min prior to procedure	Adults	Children
Amoxicillin	2 g	50 mg/kg
Cephalexin or clindamycin if penicillin allergy is present	2 g	50 mg/kg
	600 mg	20 mg/kg

Adapted from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease [14]

Table 3 Infective endocarditis prophylaxis

High-risk valvular disease conditions needing antibiotic prophylaxis against infective endocarditis
Artificial heart valves
Previous infective endocarditis
Heart transplant recipients with structurally abnormal valve regurgitation
Unrepaired cyanotic congenital heart disease with shunts
Repaired congenital defects with prosthetic material

Duval and Hoen [15]

Natural History and Complications

Mitral stenosis is generally slow to progress from asymptomatic to severe; in developed countries, rheumatic fever-associated mitral stenosis may lag 20–40 years after the presence of rheumatic disease and may take up to 10 years before the symptoms become disabling. 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 [4].

Medical Therapy and Timing of Surgery

Although medical therapies mostly consist of infective endocarditis prophylaxis and some patients may benefit from beta-blockade to decrease exertional symptoms, treatments other than surgical, whether valve replacement or PBV, have not been shown to be as effective [13] (Tables 2 and 3).

Hypertrophic Cardiomyopathy

Etiology

Fifty percent of cases of hypertrophic cardiomyopathy are familial; it is defined as hypertrophic changes that cannot be attributed to pressure changes or volume overload. This is a monogenic disease from a mutation in genes encoding components at the cellular level in the cardiac sarcomere. Global incidence is seen in 1 in 500 of the general population. Annual estimated mortality in patients with hypertrophic cardiomyopathy is 1 %. As hypertrophic cardiomyopathy is known to be an autosomal dominant genetic disorder, screening with noninvasive imaging of first-degree family members of known patients has increased our ability to assess individuals at risk for this condition [16].

Symptoms

Patients with hypertrophic cardiomyopathy may be asymptomatic their entire lifetime, or a subset of patients may present without any antecedent symptoms with a sudden death. Some patients may present with chest pains due to microvascular ischemia secondary to supply-demand mismatch from the hypertrophic myocardium. Both atrial fibrillation and progressive heart failure may result from the structural changes associated with hypertrophic cardiomyopathy [16].

Physical Findings

Although identifying patients at risk for sudden death is crucial, individuals with hypertrophic cardiomyopathy may not have identifiable physical findings, and findings when present may not be highly specific for the disease. The precordial examination may note a significant apical impulse, S3 and/or S4 may be present, and

murmurs may include a systolic ejection murmur in the aortic region that is increased when standing and decreased when squatting [5]. As a patient progresses in heart failure, the physical findings may be more easily identified but again not highly specific for hypertrophic cardiomyopathy unless noted by imaging. Although ECG with suggestive voltage criteria may indicate the presence of LVH due to hypertrophic cardiomyopathy, echocardiography and cardiac magnetic resonance imaging are the cornerstone of diagnosis. The presence of left ventricular dysfunction and the absence of other identifiable causes, especially in the presence of a contributory family history, are diagnostic for hypertrophic cardiomyopathy [16].

Natural History and Complications

Sudden cardiac death is the most devastating and unpredictable complication of hypertrophic cardiomyopathy. The presence of family history of hypertrophic cardiomyopathy-associated sudden death is the greatest predictor of risk; hypotensive blood pressure in response to exercise, unexplained syncope, episodes of ventricular tachycardia, and left ventricular hypertrophy $\geq$30 mm thickness are all considered risks for sudden cardiac death in the setting of hypertrophic cardiomyopathy. As mentioned, many individuals with hypertrophic cardiomyopathy may spend their entire lives asymptomatic. Those that have symptoms, such as heart failure or atrial fibrillation, may progress through all the stages and sequela of these conditions [16].

Medical Therapy and Timing of Surgery

A patient with concerns of hypertrophic cardiomyopathy may benefit from a cardiology consultation. Recommendations on screening of first-degree relatives and recommendations of lifestyle changes may be discussed in addition to medical management. Lifestyle adjustments are aimed at reducing the risks of sudden cardiac death and thus avoiding conditions that may impair or further exacerbate cardiac outflow. It is generally recommended that patients with hypertrophic cardiomyopathy should not participate in high-intensity physical activity. Beta-blockers or the non-dihydropyridine calcium channel blockers, verapamil and diltiazem, are the most studied and the mainstays of medical treatment for hypertrophic cardiomyopathy. Medical management of atrial fibrillation due to hypertrophic cardiomyopathy is rate control and anticoagulation, and heart failure as a sequela is also managed in a manner consistent with left ventricular failure due to other etiologies. When patients continue to have significant symptomatic outflow obstruction in the presence of optimal medical management, surgical considerations may be discussed with a specialist [16].

Murmurs During Infancy

The most common congenital anomalies are the cardiac anomalies. They occur in 0.8–1 % per 1,000 of live births and are a leading cause of death among the congenital anomalies. Early detection of pathologic heart anomalies is critical to reduce morbidity and mortality from these congenital disorders. Signs of innocent murmurs versus pathological murmurs include a murmur present only in systole, a murmur that changes with both body position and respiratory cycle, and a small area of murmur without radiations. Due to heart rate, respiratory cycle, and inability of the patient to respond to verbal instructions, in neonates, this level of auscultation may be challenging. If a murmur is consistently present and/or accompanies other signs of cyanotic structural defect, the patient should undergo echocardiography and if indicated a pediatric cardiology referral [17].

Murmurs During Pregnancy

The hemodynamic changes that are naturally occurring in pregnancy are generally well tolerated in healthy women. The cardiac output can rise from 30 % to 50 % due to changes increasing both heart rate and stroke volume. Blood volume

begins rising in the first trimester and averages 50 % more than in the nongravid state. Preconception management that assesses the lesion and addresses any recommended treatment prior to pregnancy is preferred. Even women who were previously asymptomatic may develop problems with the cardiovascular changes associated with pregnancy. Conditions that help predict risk are the location and severity of disease, the prepregnancy functional capacity, the left ventricular function, and the presence or absence of pulmonary hypertension. Stenotic lesions of the aortic or mitral valves are at the greatest risk with pregnancy-related complications. Women who present already pregnant with suspected or confirmed valvular heart disease must be evaluated as soon as possible. Transthoracic echocardiography and patient history are the principal method of gathering data and risk stratifying these patients. Low-risk conditions can be comanaged with a cardiologist; however, valvular disease with medium to high risk needs to be managed in high-risk centers with high-risk maternal fetal specialists and a specialized cardiologist [18].

Murmurs in the Athlete

The cardiovascular portion of pre-participation exam is meant to screen for the presence of lesions that may lead to sudden death. In addition to family and personal history questions regarding sudden death, exercise-induced chest pain, palpitations, dizziness, dyspnea on exertion, and syncope, the presence of abnormal auscultation is a critical portion of this exam. The presence of any of these red flags indicates a need for activity restriction, additional testing, and likely referral. In addition to auscultating a murmur in an athlete, the patient and family history and composition of the murmur help distinguish between a benign and pathological murmur. A diastolic murmur is pathologic until proven otherwise. Other pathologic signs include changes in intensity when doing physiologic maneuvers, e.g., louder with Valsalva or squat-to-stand maneuvers, loud grade three or more, holosystolic, having family history of sudden death, radiations to carotids or the axilla, and historical red flags accompanying the murmur (exertion chest pain, dyspnea on exertion, and syncope). Benign murmurs may be indicated by the absence of associated symptoms and no significant family history in addition to crescendo-decrescendo, softer sounding grade one or two, normal blood pressure, normal pulses, no significant radiation, without thrill, and early to mid-systolic in timing and no other nonphysiologic heart sounds. Red flags in either examination or history may warrant removal from play until further specialist work-up is completed and recommendations made [2].

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Heart Failure

Michael R. King

Contents

Definition

Heart failure (HF) is a clinical syndrome caused by myocardial dysfunction or death. Structurally this could result from left ventricle dilation, hypertrophy, or both. Physiologically, 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. These changes also cause HF symptoms of fluid retention, dyspnea on exertion, and fatigue. Without appropriate therapies and interventions, HF can progressively worsen [1].

Epidemiology

In 2006 there were an estimated 5.1 million people with symptomatic HF in the United States and up to 23 million worldwide. Americans over 40 years old have a 20 % lifetime risk of developing HF [1]. Because of the difficulties of defining and diagnosing HF, true prevalence estimates remain uncertain. HF does increase with age and thus is increasing in the population overall and has continued to increase in hospitalized patients. The overall prognosis of HF is poor with a 50 % mortality rate within 5 years of symptom onset.

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Table 1 ACC/AHA stages of heart failure compared to NYHA classifications

ACC/AHA Stages	NYHA Classes
Stage A: High risk, no structural heart disease	Not Applicable
Stage B: Asymptomatic but with structural heart disease (MI, remodeling, reduced LVEF, valvular disease)	**Class I:** Asymptomatic
Stage C: Current or history of symptomatic heart failure with cardiac structural abnormalities (reduced LVEF)	**Class II:** Symptoms with significant exertion
	Class III: Symptoms on minor exertion
	Class IV: Symptoms at rest
Stage D: Refractory end-stage heart failure	

Source: Yancy et al. [1]
ACC/AHA American College of Cardiology/American Heart Association, *NYHA* New York Heart Association
MI Myocardial Infarction, *LVEF* Left Ventricular Ejection Fraction

Appropriate management of HF can significantly stabilize the disease with improvement in symptoms, cardiac function, and survival [1].

Causes

Cardiac ischemia or coronary artery disease (CAD) is the most common cause of HF compromising 60–70 % of systolic HF. Heart failure is increasing in older populations because of improved survivorship from treatments of CAD and other common causes of HF including hypertension, diabetes, and valvular disease. Many other cardiac conditions can eventually cause HF: arrhythmias (atrial fibrillation/flutter, heart block), cardiomyopathies (idiopathic, hypertrophic, restrictive, postpartum), and pericarditis. Noncardiac causes should be considered as well and are discussed in the evaluation section [2].

Classification and Staging

The New York Heart Association's (NYHA) classifications are symptom based and are an established predictor of mortality in HF. Class I defines asymptomatic individuals, and Classes II, III, and IV define patients with HF symptoms with mild exertion, moderate exertion, or at rest, respectively (see Table 1). These classes are a reasonable measure of functional capacity, and a patient's class can change as their symptoms improve or worsen. In 2001, the American College of Cardiology (ACC) and the American Heart Association (AHA) created HF stages that emphasized the progression from patients at risk, Stage A; to those with structural heart disease, Stage B; to symptomatic HF with reduced ejection fraction (HFrEF), Stages C and D. Studies have shown that asymptomatic patients with reduced LVEF (Stage B) are as equally represented as symptomatic HFrEF. Table 1 demonstrates the overlap of the NYHA Classes and ACC/AHA stages [1].

Measurement of left ventricular ejection fraction (LVEF), or systolic function, is important for assessing HF and predicting mortality. Symptomatic HF with an EF <40 % defines HF with reduced ejection fraction (HFrEF), or systolic heart failure (SHF), versus an EF of >50 % that defines symptomatic HF with preserved ejection fraction (HFpEF) or diastolic heart failure (DHF) [1]. Among symptomatic patients, both are common with one study reporting 34 % had HFpEF and 66 % had HFrEF [3]. The distinction is important given that HFrEF have effective

Table 2 Accuracy of findings in diagnosing heart failure

Diagnosing heart failure	Probability	Excluding heart failure	Probability
History		**History**	
History of heart failure	+ +	No dyspnea on exertion	*
Initial clinical judgment	+		
History of myocardial infarction	+		
Paroxysmal nocturnal dyspnea	+		
Orthopnea	+		
Exam		**Exam**	
Displaced cardiac apex	+ + +	None	
Third heart sound	+ + +		
Hepatojugular reflex	+ +		
Jugular venous distension	+ +		
Rales (crackles)	+		
Peripheral edema	+		
Murmur	+		
Laboratory		**Laboratory**	
Elevated BNP/NTproBNP	+	Normal, reduced BNP/NTproBNP	**
Imaging/tracing		**Imaging/tracing**	
CXR: interstitial edema	+ + +	CXR: no venous congestion	*
Venous congestion	+ + +	No cardiomegaly	*
Cardiomegaly	+	ECG: normal	*
Pleural effusion	+		
ECG: atrial fibrillation	+		
New T-wave change	+		
Any abnormality	+		

Source: King et al. [5]
CXR chest radiography, *BNP* B-type natriuretic peptide, *NTproBNP* N-terminal pro-B-type natriuretic peptide, *ECG* electrocardiography
+++ Conclusive effect, positive likelihood ratio of >10
++ Moderate effect, positive likelihood ratio of 5–10
+ Small effect, positive likelihood ratio of 2–5
*** Conclusive effect, negative likelihood ratio of <0.1
** Moderate effect, positive likelihood ratio of 0.1–0.2
* Small effect, positive likelihood ratio of 0.2–0.5

evidence-based therapies that improve morbidity and mortality, while HFpEF do not. An ejection fraction (EF) of <45 % is a powerful predictor of mortality with an added increased risk of death with every further 10 % reduction <45 % [4].

Evaluating and Diagnosing Heart Failure

Despite being widely studied, HF remains a clinical diagnosis with no specific symptom, sign, or test clearly establishing or ruling out a diagnosis with certainty. Even more challenging is that both HFrEF and HFpEF can clinically present the same. A thorough history and examination is necessary to assess and confirm HF, investigate for other causes, and identify comorbidities. Table 2 stratifies components of an evaluation that are more beneficial and effective in diagnosing or ruling out HF compared to others with no predictive benefit.

History and Physical Exam

Dyspnea on exertion is a common symptom in HF (sensitivity 97 %) but given that it represents only 30 % of the causes of dyspnea in outpatient settings, it is not specific [5]. Orthopnea, paroxysmal nocturnal dyspnea, and edema are more helpful symptoms, having a small benefit in diagnosing

Table 3 Laboratory evaluation for heart failure and selected alternate causes

Initial labs	Causes or alternate diagnosis
BNP or NTproBNP	Heart failure
Complete blood counts	Infection, anemia
Hemoglobin A1C	Diabetes
Lipid profile	Hyperlipidemia, cardiovascular risk
Liver function (transaminases)	Hepatic congestion, liver disease, alcoholism, drug toxicity
Renal function (blood urea nitrogen, creatinine)	Renal disease, volume overload
Serum electrolytes (sodium, potassium, calcium, magnesium)	Diuretic therapies, arrhythmias
Thyroid stimulating hormone	Hyper/hypothyroid disease
Urinalysis (proteinuria, hematuria, casts)	Renal disease, nephrotic syndrome, glomerulonephritis

Other labs	Causes or alternate diagnosis
Arterial blood gases	Hypoxia or pulmonary disease
Blood cultures	Bacterial endocarditis, systemic infection
Erythrocyte sedimentation rate, C-reactive protein	Infection, rheumatologic diseases
Human immunodeficiency virus	Cardiomyopathy
Ferritin, iron levels, transferrin saturation	Hemochromatosis, macrocytic anemia
Lyme serology	Bradycardia/heart block
Thiamine	Deficiency, beriberi, alcoholism
Troponins, creatine kinase-MB	Myocardial infarction or myocardial injury
Urine or serum drug screens	Illegal drug use, cocaine

Sources: King et al. [5], McMurray et al. [2], and Pinkerman et al. [8]
BNP B-type natriuretic peptide, *NTproBNP* N-terminal pro-B-type natriuretic peptide

HF (see Table 2) [5, 6]. Although not predictive, reduced exercise capacity, nocturnal cough, and peripheral or abdominal swelling are suggestive of HF. Early satiety, nausea, vomiting, abdominal discomfort, wheezing, cough, fatigue, generalized weakness, and confusion can also be suggestive of HF but are often found in other diagnosis [7].

A careful physical examination can assess the degree of hypervolemia, ventricular enlargement, and reduced cardiac output with HF. A third heart sound (S3 or ventricular gallop) is the most specific and conclusive finding for elevated left ventricular systolic pressures and decreased LVEF (specificity of 99 %). A displaced cardiac apex is also a conclusive finding in the diagnosis of HFrEF. Similar findings that are moderately beneficial in diagnosing include increased jugular venous distention and a hepatojugular reflex (see Table 2) [5, 6]. Other physical exam findings can help assess alternate causes of HF. Cardiac murmurs suggest primary valvular disease. Irregular heart rate or pulses can suggest arrhythmias or atrial fibrillation. Thyromegaly or goiter can indicate thyroid disease. Hepatomegaly can suggest cirrhosis and portal hypertension that can cause volume overload. Other findings can help to assess other differential diagnosis. On pulmonary exam, rhonchi or wheezing can suggest COPD, asthma, or pneumonia, and dullness to percussion can also suggest pneumonia or a pleural effusion [2, 8].

Laboratory and Imaging

An initial laboratory assessment can be useful to evaluate for other differential diagnosis and exclude other causes of HF (see Table 3). Further laboratory assessment should be considered based on suspicion of other causes or if findings suggest further investigation.

B-Type Natriuretic Peptide

B-type natriuretic peptide (BNP) is a cardiac neurohormone that is secreted from the ventricles in response to stretching and increased wall tension from volume and pressure overload. Both BNP and N-terminal pro-B-type natriuretic peptide (NTproBNP), an inactive cleaved fragment of proBNP, are useful in the diagnosis of HF in patients presenting with dyspnea. Although no BNP threshold indicates the presence or absence of HF with certainty, multiple systematic reviews

Table 4 BNP and NTproBNP values and outcomes

Outcome	BNP, pg/ml	NTproBNP, pg/ml
Exclude heart failure	<100	<300
Diagnose heart failure	>400	>450, age <50
		>900, age 50–75
		>1,800, age >75
In acute heart failure:	>200	>5,180
Increased 60–90 day cardiovascular events and mortality		
Outpatient heart failure goals:	<100	<1,700
Reduced exacerbations, hospitalization, and mortality		

Sources: Maisel [23], Januzzi et al. [11], Balion et al. [9], and Chen et al. [12]
BNP brain natriuretic peptide, *NTproBNP* N-terminal pro-B-type natriuretic peptide

have shown normal or low levels of BNP or NTproBNP (see Table 4) which can effectively rule out a HF diagnosis (negative likelihood ratio 0.10 and 0.14). Higher values of both have reasonably high positive predictive value of a HF diagnosis, and as the value rises the specificity rises [9–11].

When evaluating HF, providers should be aware that BNP and NTproBNP elevations can be associated with many cardiac (acute coronary syndrome, valvular heart disease, atrial fibrillation, and pericardial disease) and noncardiac causes (older age, anemia, renal failure, pulmonary disease, and sepsis) [1]. Overall, BNP levels do appear to have better reliability than NTproBNP, especially in older populations [12, 13].

The level of BNP and NTproBNP can be useful in establishing the prognosis and severity of HF in acute and outpatient settings [1]. In acute HF, an elevated BNP or NTproBNP (see Table 4) can be a strong predictor of 90-day cardiovascular events and mortality [9, 11, 12]. During a hospitalization, a 30–50 % reduction in patient BNP levels at hospital discharge compared to admission has been shown to lead to improved survival and reduced rehospitalization [12]. Levels of BNP and NTproBNP can improve or lower with appropriate outpatient treatment of chronic HF and appear to correlate with improved clinical outcomes. These observations have led to studies of BNP- or NTproBNP-guided therapies that have shown some inconsistent results. Further meta-analyses reviews, however, have concluded that BNP- or NTproBNP-guided therapy reduces all-cause mortality in acute and chronic HF compared to usual care [11]. Specifically, optimizing management for specific outpatient targets of BNP or NTproBNP (see Table 4) has resulted in improvements in HF decompensations, hospitalizations, and mortality [9, 12].

Electrocardiogram

An electrocardiography (ECG) is a useful initial test to evaluate the heart for structural or physiological abnormalities. The presence of atrial fibrillation, new T-wave changes, or any abnormality has a small benefit in effectively diagnosing HF [14]. A normal ECG or one with only minor abnormalities has a small benefit in effectively ruling out HFrEF or systolic HF (see Table 2) [14]. An ECG is most useful in evaluating other possible causes of HF or reasons for a worsened clinical status. 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 increased 1-year mortality overall and from sudden cardiac death [15]. 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.

Chest Radiograph

Patients with suspected HF or acute decompensation should receive a chest radiograph to assess pulmonary congestion, possible cardiomegaly, or alternate cardiac or pulmonary causes of symptoms [1]. The presence of interstitial edema and venous congestion is more beneficial in effectively diagnosing HF with specificities of 96 % and 97 %, respectively. Other findings such as cardiomegaly and a pleural effusion only have a small benefit in diagnosing HF. The absence of

cardiomegaly and venous congestion only slightly decreases the likelihood of HF (see Table 2) [5]. Other potential causes of dyspnea symptoms that can be identified by chest radiograph include pneumonia, COPD, pneumothorax, or a pulmonary mass.

Cardiac Imaging

Echocardiogram (ECHO) remains the method of choice for evaluating suspected HF given its accuracy, availability, safety, and cost. With Doppler imaging, it can provide important information about cardiac anatomy and function including LVEF, wall motion, valvular function, right ventricular function, pulmonary artery pressures, and the pericardium. ECHO is the usual standard for assessing LVEF and differentiating HFrEF (systolic failure) versus HFpEF (diastolic failure). There is no single ECHO parameter sufficiently accurate and reproducible to diagnose left ventricular diastolic dysfunction. Given the lack of consensus, the diagnosis of diastolic dysfunction should result from multiple findings by ECHO [7].

Evaluation for ischemic heart disease in HF with stress echocardiography or nuclear stress imaging is warranted when angina is present given that CAD is the most common cause of HF.

If evidence of ischemia exists, a cardiology referral may be appropriate to consider further evaluation and treatment. Coronary angiography remains an important consideration in patients with angina, those suitable for coronary revascularization, or those with evident reversible myocardial ischemia. In instances of acute HF with pulmonary edema or shock, coronary angiography may be required urgently if acute coronary syndrome is suspected. Cardiac MRI, although not readily available, provides most of the anatomical and functional assessment of ECHO but also can evaluate ischemia and identify inflammatory or infiltrative causes of HF without radiation exposure [2].

Treatment of Heart Failure

Treatment options for HFrEF, ACC/AHA Stages C and D, have been well researched and analyzed compared to HFpEF, and there is reasonable consensus about treatment among expert societies' guidelines.

Heart Failure with Reduced Ejection Fraction

The goals of treatment in HFrEF are to improve symptoms and quality of life, slow the progression or reverse cardiac dysfunction, and improve long-term morbidity and mortality [7]. The standard therapy for HFrEF accomplishes these goals with loop diuretics for fluid and symptom control as well as angiotensin-converting enzyme inhibitor (ACEI), or an angiotensin receptor blocker (ARB) if ACEI intolerant, and beta-blocker therapy to improve morbidity and mortality. Further treatment options should be added based on the appropriate evidence and indications to control symptoms or enhance long-term survival (see Table 5). Appropriate starting doses of drug therapies and evidence-based targets are listed in Table 6.

Diuretics

Loop diuretic therapy is necessary in both HFrEF and HFpEF for managing symptoms and maintaining fluid control. They act to increase sodium excretion by 20–25 % and thus enhance free water clearance and reverse the volume expansion of HF that occurs from renotubular sodium retention after activation of the renin-angiotensin-aldosterone system. Loop diuretics can improve symptoms of pulmonary and peripheral edema within hours but are not sufficient for long-term clinical stability without other indicated therapies. 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 appropriate dose titration is achieved once a patient actively diuresis >500–1,000 mL/h. If the effect is not achieved, the dose should be increased or doubled to effectiveness. Furosemide (Lasix) is the most commonly used loop diuretic, but furosemide (Demadex) or bumetanide (Bumex) may be an option if a longer duration of action and more predictable absorptions are

Table 5 Evidence-based therapies and benefits for heart failure with reduced ejection fraction

Recommendation	Evidence-based therapies	Benefits of therapy
Beneficial, effective, recommended	Loop diuretics[c] – titrate to appropriate diuretic response for fluid control and symptom relief (dyspnea, edema)	Relieve signs and symptoms of congestion/volume overload
	Standard therapy for all HF patients, LVEF≤40	
	ACEI[a] – initiate low dose, titrate target doses ARB[a] – if ACEI intolerant, initiate low dose, titrate to target doses	Reduces morbidity (31 % RRR in hospitalizations) and mortality (17 % RRR, NNT* 26)
	β-Blockers[a] – initiate early with low-dose ACEI and titrate to target for dose-dependent benefit	Reduces morbidity (41 % RRR in hospitalizations) and mortality (34 % RRR, NNT* 9)
	In selected patients, on standard therapy	
	Aldosterone antagonists[a] – in NYHA II–IV, LVEF≤35, with persist symptoms	Reduces morbidity (35 % RRR in hospitalizations) and mortality (30 % RRR, NNT* 6)
	Hydralazine and isorbide dinitrate[a] – in African-American, NYHA III–IV, with persistent symptoms	Reduces morbidity (33 % RRR in hospitalizations) and mortality (43 % RRR, NNT* 7)
	ICD[a] – in LVEF≤35, >1 year life expectancy	Reduction in sudden cardiac death
	CRT[a] – in LVEF≤35, sinus rhythm, LBBB, QRS >150 ms, NYHA II[b] or III–IV	Reduces morbidity and mortality
Reasonably beneficial, probably recommended	**In selected patients**	
	Dietary sodium restriction[c]	Reduces symptoms
	ARB[a] – first line, in post-MI, instead of ACEI	Reduces morbidity and mortality
	Hydralazine and nitrates [b] – ACE/ARB intolerance	Reduces morbidity and mortality
	Digitalis[b] – only if persistent symptoms	Reduces symptoms and hospitalizations
	CPAP[b] – heart failure and sleep apnea	Increases LVEF and improves function
	Cardiac rehabilitation[b]	Improves function, quality of life, and mortality
	Omega-3 polyunsaturated fatty acid (PUFA)[b]	Reduces mortality and hospitalizations

Source: Yancy et al. [1]

ACEI angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *CPAP* continuous positive airway pressure, *CRT* cardiac resynchronization therapy, *ICD* implantable cardioverter defibrillator, *LBBB* left bundle branch block, *LVEF* left ventricular ejection fraction, *MI* myocardial infarction, *NNT** number needed to treat (standardized to 36 month), *NYHA* New York Heart Association, *RRR* relative risk reduction

[a]Level of evidence A (multiple randomized trials, meta-analysis)

[b]Level of evidence B (single randomized or nonrandomized trials)

[c]Level of evidence C (expert opinion, case studies, standard of care)

needed. Initial, maximum, and equipotent oral and intravenous (IV) dose equivalents are listed in Table 6. The frequency of dosing (daily or multiple times a day) should be guided by the need for more frequent diuresis to maintain an appropriate fluid volume and body weight. Being too aggressive can lead to overdiuresis and adverse renal effects.

Angiotensin-Converting Enzyme Inhibitor

ACEI therapy is indicated for all NYHA classes and ACC/AHA stages of HF. In HFrEF, ACEIs improve symptom control, mortality, and reduce hospitalizations as proven in multiple randomized controlled trials, meta-analysis reviews, and long-term studies. The benefit of ACEI therapy appears

Table 6 Medications in heart failure with reduced ejection fraction

Drugs for mortality and morbidity benefit	Initial doses	Target doses
Angiotensin-converting enzyme inhibitors		
Captopril (Capoten)	6.25 mg TID	50 mg TID
Enalapril (Vasotec)	2.5 mg BID	10–20 mg BID
Fosinopril (Monopril)	5–10 mg daily	40 mg daily
Lisinopril (Zestril, Prinivil)	2.5–5 mg daily	20–40 mg daily
Perindopril (Aceon)	2 mg daily	8–16 mg daily
Quinapril (Accupril)	5 mg BID	20 mg BID
Ramipril (Altace)	1.25–2.5 mg daily	10 mg daily
Trandolapril (Mavik)	1 mg daily	4 mg daily
Angiotensin receptor blockers		
Candesartan (Atacand)	4–8 mg daily	32 mg daily
Losartan (Cozaar)	25–50 mg daily	50–100 mg daily
Valsartan (Diovan)	20–40 mg BID	160 mg BID
β-Blockers		
Bisoprolol (Zebeta)	1.25 mg daily	10 mg daily
Carvedilol (Coreg)	3.125 mg BID	50 mg BID
Carvedilol CR (Coreg CR)	10 mg daily	80 mg daily
Metoprolol succinate CR/XL (Toprol XL)	12.5–25 mg daily	200 mg daily
Aldosterone antagonists		
Eplerenone (Inspra)	25 mg daily	50 mg daily
Spironolactone (Aldactone)	12.5–25 mg daily	25 mg daily or BID
Vasodilators: hydralazine and isosorbide dinitrate		
Fixed dose hydralazine and isosorbide dinitrate (BiDil)	37.5 mg/20 mg TID	75 mg/40 mg TID
Hydralazine and isosorbide dinitrate (Apresoline and Isordil)	25–50 mg and 20–30 mg TID or QID	300 mg and 120 mg daily in divided doses

Drugs for symptom control		Initial doses	Maximum doses
Loop diuretics	**Drug/dose equivalents**		
Bumetanide (Bumex)	1 mg PO/1 mg IV	0.5–1.0 mg/dose	10 mg/day
Furosemide (Lasix)	40 mg PO/80 mg IV	20–40 mg/dose	600 mg/day
Torsemide (Demadex)	20 mg PO/20 mg IV	5–10 mg/dose	200 mg/day
Thiazide diuretics (combination with loops)			
Hydrochlorothiazide (HydroDiuril)		25 mg daily	100 mg daily
Metolazone (Zaroxolyn)		2.5 mg daily	10 mg daily
Inotrope			
Digoxin (Lanoxin)		0.125 mg daily	0.125–0.375 mg daily

Source: Yancy et al. [1]
IV intravenous, *PO* oral, *BID* twice daily, *TID* three times daily, *QID* four times daily

to be a class effect with all ACEIs being equally effective in improving HF outcomes by inhibiting the renin-angiotensin-aldosterone system that is activated in HF. Guidelines recommend titrating to achieve a target dose (see Table 6) based on the clinical research but lower doses appear to have mortality benefits [1].

Beta-Blockers

Beta-blockers are a standard therapy indicated as an initial treatment for all patients with current or prior symptoms of HFrEF (NYHA Classes II–IV, LVEF <40), unless contraindicated, to reduce morbidity and mortality. 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. The COMET trial showed carvedilol (Coreg), an apha-1, beta-1, and beta-2 receptor inhibitor, reduced HF mortality by 40 % compared to 34 % by twice daily, immediate-release metoprolol tartrate (Lopressor), a beta-1 selective inhibitor [16]. Carvedilol (Coreg) proved an obvious benefit; however, this study did not use the previously studied once-daily sustained release metoprolol succinate (Toprol XL), a more reasonable comparison. Importantly, the study did prove a survival benefit, albeit lower, with metoprolol tartrate (Lopressor).

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 (see Table 6). The dose should be doubled every 2–3 weeks until target doses and heart rate reductions in proven clinical trials are achieved given the dose-dependent survival and outcome improvement [1]. A meta-analysis review showed that for every five beats per minute reduction in heart rate, there was an 18 % reduction in risk of death [17].

Beta-blockers can cause a 4–10-week increase in symptoms before benefits are realized; thus patients should be hemodynamically stable with minimal to no fluid retention before initiation. Beta-blockers are contraindicated with bradycardia, hypotension, hypoperfusion, second- or third-degree atrioventricular block, or severe asthma or COPD [1].

Angiotensin Receptor Blockers

ARBs are indicated for patients intolerant to ACEIs and have been well studied and proven to be as effective as, but not superior to, ACEIs at improving HF symptoms, mortality, and morbidity. In general, ACEI therapy is considered first-line therapy given the large amount of evidence validating them compared to ARBs. Recent guideline recommendations do suggest ARBs are a reasonable first-line alternative to ACEIs if patients are already taking ARBs for other indications. Systematic reviews have not found an outcome benefit to combined ACEI and ARB therapy and it is not generally recommended but there is limited evidence to support considering the combination in patients with persistent symptoms who cannot take an aldosterone antagonist [1].

Aldosterone Receptor Antagonists

Aldosterone receptor antagonists, or mineralocorticoid receptor antagonists (MRAs), are recommended in NYHA Class II–IV patients who have LVEF ≤35 %. Both spironolactone (Aldactone) and eplerenone (Inspra) improve symptoms and mortality as well as reduce HF hospitalizations when added to standard therapy (see Table 5). MRAs block aldosterone's effects to cause vasoconstriction and volume expansion by sodium reabsorption and potassium excretion in the distal tubule and collecting ducts. A creatinine of <2.5 mg/dL in men or <2.0 mg/dL in women (or GFR >30 mL/min) and a potassium of <5.0 mEq/L are important to avoid the substantial risk of hyperkalemia and renal insufficiency. Careful monitoring of these levels is important at initiation or after a change in therapy. The routine use of an ACEI, ARB, and MRA in combination is potentially harmful and should be avoided [1].

Hydralazine and Nitrates

The vasodilator hydralazine and isosorbide dinitrate combination therapy (see Table 6) is recommended in self-described African-

American patients with HFrEF and NYHA Class III–IV symptoms receiving optimal therapy with ACEI, beta-blocker, and MRA, unless contraindicated [1]. The combination reduces symptoms, quality of life, HF hospitalization, and mortality as shown in the African-American HF Trial (A-HeFT) [18]. Guidelines also suggest a benefit to utilizing the combination in patients who cannot take ACEIs or ARBs due to intolerance, hypotension, or renal insufficiency [1].

Digoxin

Digoxin therapy is reasonable and beneficial for symptom control and to reduce hospitalizations in patients on standard therapy or for rate control in HF and atrial fibrillation [1]. Studies have not proven a mortality benefit, and mortality can worsen with serum digoxin levels >1.2 ng/mL. A level of <1.0 ng/mL is considered therapeutic and should be monitored 1–2 weeks after initiation. Digoxin is renally excreted, and toxicity risk is higher in elderly patients with renal dysfunction and in patients with hypokalemia and hypomagnesemia which are both common in HF patients. Withdrawing digoxin therapy can lead to clinical deterioration and should be done cautiously [8].

Adverse Therapies

Anticoagulation therapy is not recommended in HF without a history of atrial fibrillation/flutter or a history of a thromboembolic event given the significant risk of bleeding. Similarly, antiplatelet therapy, including aspirin, has bleeding risks and has not been proven beneficial and can interfere with HF therapies [1]. Nondihydropyridine calcium channel blockers (e.g., diltiazem [Cardizem] and verapamil [Calan]) have proven to worsen HF symptoms given their negative inotropic effects. Dihydropyridine calcium channel blockers (e.g., amlodipine [Norvasc] and felodipine [Plendil]) appear safe but are only recommended for hypertension control. Drugs that increase salt and fluid retention (nonsteroidal antiinflammatory drugs [NSAIDS], steroids, and thiazolidinediones) can worsen clinical status in HF and should be avoided if possible. NSAIDS can also increase the risk of thrombotic events and cause peripheral vasoconstriction in HF. Phosphodiesterase inhibitors should be used with caution given the risk of hypotension. Many of these drugs are commonly prescribed but given their adverse risks in HF, they should be used with caution or avoided [1].

Implantable Devices

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 implantable cardioverter defibrillators (ICDs) are indicated for primary and secondary prevention. In primary prevention, ICDs are recommended for HF patients with a reasonable life expectancy (>1 year) and no history of recent MI (within 40 days). The other criteria includes patients with NYHA Class II–III and a LVEF ≤35 % or NYHA Class I and a LVEF <30 % [1]. Multiple studies have proven the benefit in NYHA Class II–III reducing mortality by 23–31 % [2]. In patients with a history of cardiac arrest, ventricular fibrillation, or hemodynamically destabilizing ventricular tachycardia, an ICD is recommended regardless of EF for secondary prevention of SCD [1].

Ventricular dyssynchrony can occur as HF progresses given that 30–50 % of HF patients have interventricular conduction delay [7]. As a result, cardiac resynchronization therapy (CRT) with biventricular pacing is indicated for patients with NYHA Class III or IV symptoms, a LVEF ≤35 %, a QRS interval ≥0.15 ms, a left bundle branch block (LBBB) pattern, and sinus rhythm to improve mortality and hospitalizations. Studies of CRT vary to include NYHA Class II, a QRS ≥0.12 ms (the level defining dyssynchrony), 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].

Heart Failure with Preserved Ejection Fraction

In most patients with systolic HF, diastolic dysfunction is also present. In studies of clinical HF,

approximately 50 % of patients have HF*p*EF [19]. Although debated, the definition of HFpEF includes clinical signs or symptoms of HF, preserved or normal LVEF, and evidence of abnormal left ventricular diastolic dysfunction by Doppler ECHO or cardiac catheterization. Specifically, these findings are evidence of impaired left ventricular diastolic filling with increased end-diastolic pressures and a stiff left ventricle with decreased compliance and impaired relaxation. The increased end-diastolic pressures of the left ventricle lead to pulmonary congestion, dyspnea, and other HF symptoms. There is not a consistent agreement on Doppler ECHO criteria for diastolic dysfunction, and at times the results are inconclusive; thus cardiac catheterization remains the gold standard to directly measuring ventricular diastolic pressure [20, 21]. Hypertension is the most important cause of HFpEF with a prevalence of 60–89 %. Patients are likely to be older women with hypertension, obesity, CAD, diabetes mellitus, atrial fibrillation, and hyperlipidemia [19]. Overall with HFpEF, no treatment has been well validated to show a reduction in morbidity and mortality, thus most recommendations are only expert opinion. Blood pressure should be controlled by national guidelines utilizing beta-blockers, ACEI, and ARBs to prevent morbidity, and diuretics should be used for relief of volume overload symptoms [1]. Two very small studies showed the heart rate-limiting calcium channel blocker verapamil (Calan) may improve exercise capacity and symptoms in patients with HFpEF. ACEI and ARB therapy are recommended but limited studies have not shown a definitive reduction in cardiovascular death or HF hospitalizations [2].

Acute Heart Failure Syndrome

Acute heart failure syndrome (AHFS) is a life threatening condition that requires immediate medical attention usually leading to admission to the hospital or intensive care unit. AHFS can occur during an initial diagnosis or arise as a result of deterioration of chronic HF, either HFrEF or HFpEF. Patients can have all the symptoms and findings of chronic HF but also have pronounced volume overload with peripheral and pulmonary edema. This can be a potentially fatal cause of acute respiratory distress with severe dyspnea and hypoxia that can lead to cardiogenic shock. A careful history for precipitating factors and prior exacerbations should be obtained. Diuretic noncompliance often contributes, thus a careful history of medications, dose and frequency of use is helpful. Acutely worsened coronary ischemia, valvular function, or arrhythmias can cause severe HF decompensations. Many noncardiac causes can lead to AHFS: severe hypertension, acute pulmonary edema, chronic lung disease, renal disease, anemia, or infection [2]. In addition to a normal HF evaluation, an arterial blood gas is warranted to accurately assess acid-base abnormalities. 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 [2]. Hypoxemia in AHFS is associated with increased risk of mortality thus should be treated if the SpO2 $<$90 %. Noninvasive positive pressure ventilation (NIPPV) should be considered in dyspnea patients with pulmonary edema when the respiratory rate is $>$20 breaths/min whether they have hypoxia or not. NIPPV has proven to decrease the likelihood of intubation, improve respiratory status and dyspnea, and reduce hypercapnia and acidosis. Mechanical ventilation should be considered if NIPPV cannot be utilized or is contraindicated [1]. IV 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 outtake, 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 [1].

IV vasodilators, nitroglycerin or nitroprusside (Nitropress), are recommended for persistent congestive symptoms and rapid symptom relief in acute pulmonary edema or severe hypertension not responding to diuretics alone. Blood pressure should be monitored closely and the doses decreased if symptomatic hypotension or worsening renal function occurs [7]. IV inotropic agents such as dobutamine or milrinone (see Table 6) are indicated in AHFS when LVEF is reduced and hypotension (systolic blood pressure $<$90 mmHg) causes diminished perfusion and end-organ dysfunction (low-output syndrome). Invasive hemodynamic and heart monitoring are needed to evaluate heart filling pressures, cardiac index, and possible arrhythmias. When initiating a vasodilator or inotropic therapy, consideration should be given for cardiology or pulmonary consultation. Once hemodynamically stable, the initiation of standard evidence-based therapies for chronic HF is indicated [7].

Counseling and Self-Management

Counseling patients with HF education and strategies for self-care are critically important to enhance treatment compliance and manage worsening signs and symptoms of fluid retention. Counseling and education are also important to improve transitions of care given that HF patients are frequently hospitalized. 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 healthcare 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. In patients with HF and sleep apnea, compliance with continuous positive airway pressure (CPAP) is important to increase LVEF and improve functional status [8].

Prevention

The ACC/AHA Stages A and B do not have symptomatic HF but represent an opportunity for prevention given the risk of developing HF. Stage A patients have normal heart structure and function, and evidence-based disease management of high-risk HF conditions such as hypertension, lipid disorders, diabetes mellitus, obesity, and thyroid disease and secondary prevention of atherosclerotic vascular disease based on current guidelines are recommended.

Controlling hypertension can reduce the rates of HF by 50 %. Because of their strong cardiovascular benefits, ACEIs or ARBs (if ACEI intolerant) are recommended in patients with known atherosclerotic vascular disease or diabetes. Behavior changes including tobacco cessation, regular exercise, and avoidance of alcohol and illicit drug use are also recommended to reduce risk [1].

Stage B patients already have cardiac structural abnormalities including previous MI, evidence of left ventricular remodeling (left ventricular hypertrophy or reduced LVEF), or valvular disease. These individuals' risk of HF progression is significantly higher, and treatments that preserve heart function are a priority. In those with a previous history of MI, ACEIs, ARBs, and beta-blockers are proven effective in reducing overall mortality, cardiovascular death, and symptomatic HF. Evidence-based management of CAD, MI, and chronic angina can further decrease the progression to symptomatic HF [1]. Patients with nonischemic cardiomyopathy, a reduced LVEF with no history of MI, also benefit from ACEI or ARB therapy. The SOLVD study showed a 37 % reduction in the development of symptomatic HF with ACEI therapy. The benefit or ACEI was retained in the same 12-year follow-up study in which ECHO data showed that ACEIs inhibit left

ventricular remodeling by attenuating worsening left ventricular dilation and hypertrophy [22]. Beta-blocker therapy has less evidence to support their benefit but is recommended given many patients will have other indications [1].

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Cardiovascular Emergencies

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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 we must be able to recognize and assess them. Furthermore, Family Physicians will continue to care for these patients as they live with these conditions. Our patients will turn to us 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, 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.

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. Myocarditis, endocarditis, cardiomyopathy, and contusion after chest wall trauma can also cause cardiogenic shock.

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

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 [3]. This further widens the gap between oxygen needs 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) or elevated pulmonary capillary wedge pressure $>$ 15 mmHg [3].

Despite numerous advances in revascularization, medication, and mechanical support, cardiogenic shock is still the number one cause of mortality due to acute MI (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 [4].

Patients who develop cardiogenic shock during a hospitalization for AMI are more than 10 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, female, have a do-not-resuscitate 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 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 ie SBP> 80 mm Hg in conjunction with vasodilators [5].

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 does coronary artery bypass grafts (CABG) if the patient has suitable coronary anatomy [4]. 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 2010, and the American Heart Association (AHA) Guidelines for CPR and ECC were updated.

In a major shift, the usual "ABC's" 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 that oxygen demand is lessened during cardiac arrest and therefore pumping blood to a victim's brain is more important than oxygen [6]. In fact, bystander Hands-Only CPR, where compressions are done without breaths, shows similar outcomes to conventional CPR in adults [7].

The compression rate has been changed from "approximately 100 compressions per minute" to "at least 100 compressions per minute."

Compression depth is now 2 in. for adults as opposed to 1½ to 2 in. for adults. The depth has changed for children as well [8].

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.

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 III	Originates in the descending aorta

Table 3 Standford classifications

Type A	All dissections that involve the ascending aorta
Type B	All dissections that do not involve the ascending aorta

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).

Aortic Dissection

Classification

There are two classification systems used: De Bakey and Standford (see Tables 2 and 3).

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 vaso vasorum into the media of the aortic wall. This can happen either spontaneously or by a penetrating atherosclerotic ulcer [9].

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, and crack cocaine use can all contribute to aortic dissection.

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 [10].

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 [11].

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 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) was used in 2 %, and Angiography was used in 4 %. For confirmation or further evaluation, TTE/TEE was used 56 %, CT 18 %, MRI in 9 %, and angiography in 17 % [11].

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 [10].

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 [10]. This may be a concern in smaller centers where aortic dissection isn't diagnosed frequently.

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 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. [5D] 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 % [10, 12]. 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 should be 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 % [12]. The overall mortality rate for Type B dissections treated medically was 10.7 % in the International Registry of 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 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 [10]. About 25 % of Type B dissections are complicated at presentation [12].

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 [13]. 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 [14].

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, Neurally mediated, Neurologic, Orthostatic, or Psychogenic (see Table 4).

The differential for syncope includes seizures, dizziness, presyncope, drop attacks, vertigo, and near sudden cardiac death events [15]. 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 (post-ictal 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 [16]. Urinary or fecal incontinence can be seen with either condition but are 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

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
Neurally mediated	Vasovagal, situational, micturition, defecation, sight of blood	24	None
Neurologic	Steal syndrome, TIA's, 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 %

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 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 or aortic stenosis is 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 7 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 % [17].

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 cardiac arrhythmia as opposed to those with three or four of these risks who had a 58–80 % chance [17].

History and Physical Exam

In diagnosing and distinguishing between types of syncope, history, and physical exam allow for more accurate diagnosis than any other modality, establishing the diagnosis between 14 % and 25 % of the time. 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. 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 [17]. 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 [16]. 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), bundle branch block(BBB), particularly right BBB with ST elevation which is seen in Brugada syndrome. One should also look for ST-elevations suggestive of myocardial infarction, bradycardia, seconnd 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 [16].

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 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 [17].

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 cardiac 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 US than stroke, lung cancer, and breast cancer combined. Worldwide, it is responsible for 50 % of overall cardiac deaths [18]. 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 4–7 fold higher risk of SCD in men than women < 65. After age 65, the ratio of SCD in men to women is 2:1 or less [18]. Before menopause woman have 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.

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 EF's < 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 cardiomyopathy. The American College of Cardiology (ACC), American Heart Association (AHA), and the Heart Rhythm Society (HRS) published guidelines recommending ICD implantation in people with ejection fractions less than 30–35 % with heart failure [19]. 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 U.S. 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 [20]. 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.

Once 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 [20].

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.

Implantable cardiac defibrillators (ICD's) 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 [20]. 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

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Introduction

Deep vein thrombosis (DVT) and pulmonary embolism (PE) have a shared pathophysiology and together, along with superficial thrombophlebitis, comprise the spectrum of venous thromboembolism (VTE). PE causes 10 % of deaths in hospitals representing the most common preventable cause of death in patients with misdiagnosed or improperly treated DVT [1]. **Evaluating** the patient's history, signs, symptoms and risk factors for VTE is essential for diagnosis along with the use of validated clinical prediction rules. Once diagnosed, multiple effective treatment options are currently available, including well-tolerated new oral anticoagulants, for short- and long-term treatment.

Pathophysiology

Inflammation and Virchow's Triad of endothelial injury, hemodynamic changes (such as stasis or turbulence) and hypercoagulability are the classic elements that bring about thrombosis. 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 [2]. 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 [2]. Endothelial injury and stasis also increase VTE risk via increasing coagulation factors and preventing adequate mixing of anti-clotting factors, respectively [2, 3]. Local injury from indwelling devices, such as pacemaker leads or long-term indwelling central venous catheters, also increase upper extremity DVT formation [3].

Inherited and acquired thrombophilias affecting anticoagulant or pro-coagulant pathways lead to hypercoagulopathy [4]. 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 [5]. Antiphospholipid antibody syndrome is an acquired autoimmune disorder characterized by antiphospholipid and anticardiolipin antibodies that increase the risk of recurrent VTE [6].

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. Some consensus recommendations encourage screening for anyone diagnosed with VTE under 40 year old, others, including the American College of Chest Physicians, argue against testing [7]. Evidence suggests that family history of unprovoked VTE in a first-degree relative, especially when under 50 year old, may be more important for counseling patients (i.e., pregnancy) on their inherent risk than specific testing results [8].

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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

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Epidemiology

Approximately 900,000 new onset or recurrent PE or DVT cases occur annually, with 60,000–300,000 VTE events resulting in death each year. VTE accounts for approximately 1 % of hospital admissions in the US annually, while two-thirds of VTE cases occur in patients who have been hospitalized within the past 90 days [5]. Hospitalization, acute and chronic illness with resulting inflammation, recent surgery, and pregnancy or chemotherapy can all increase the risk of VTE up to 100 fold [4, 5]. The increased risk with cancer is multifactorial, but very evident. Tumors activate coagulation or may compress veins causing stasis. The incidence of VTE during the first 6 months after a cancer diagnosis is 12.4 per 1,000 [5, 9].

Modifiable risk factors for VTE include obesity, hypertension, tobacco use, dyslipidemia, diabetes, diet, stress, hormone replacement and contraceptive use. Patients with a BMI > 30 have a two to three fold higher risk, and may be related to impaired venous return or increased coagulation and inflammation [5]. Age-adjusted VTE incidence is highest among Caucasians (108 per 100,000) followed by African-Americans (78 per 100,000) then Asian and Native Americans [4, 5]. The rate of VTE increases exponentially with age, and may be associated with the biology of aging rather than increasing risk factor exposure. The most significant complications of VTE are venous stasis syndrome, venous ulcers and chronic thromboembolic pulmonary hypertension. The 20 year cumulative incidence of stasis syndrome after VTE and proximal DVT are 25 % and 40 % respectively, while that of venous ulcer is 3.7 % [4].

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Table 2 Well's 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 along 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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Diagnosis

Evaluating the history, signs, symptoms and the individual's risk factors for VTE are essential for diagnosis (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 chest pain, tachypnea, tachycardia, dyspnea and cough. Concurrent DVT symptoms may also be present in those with suspected PE. Congestive heart failure (CHF), acute coronary syndrome (ACS), and chronic obstructive pulmonary disease (COPD) share similar signs and symptoms as PE and may confound the diagnosis [10].

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 [11]. The American College of Chest Physicians (ACCP), American College of Physicians (ACP), American Academy of Family Physicians (AAFP) and the Institute for Clinical Systems Improvement (ICSI) all support use of validated clinical prediction rules to assess pretest probability of VTE to guide diagnostic decision making [11–14].

A variety of formal scoring systems have been developed and validated to assist in stratifying patients with suspected DVT or PE [10]. Well's criteria is frequently used for DVT assessment and assigns a pretest probability category based on risk factor scoring (Table 2). Well's PE criteria and the modified Geneva criteria have similar predictive value and assist providers in determining pretest probability for PE [15]. For Well's PE criteria, the physician assigns points for different clinical criteria which include: signs and symptoms of DVT (i.e., leg swelling and calf tenderness), 3 points; diagnosis of PE at least as likely as an alternative diagnosis, 3 points; prior documented history of PE or DVT, 1.5 points; recent surgery (past 4 weeks) or immobilization for greater than 2 consecutive days, 1.5 points; pulse rate greater than 100 beats/min, 1.5 points; hemoptysis, 1 point; and active or recent (past 6 months) cancer history, 1 point. A patient's pretest probability is considered low for scores less than 2, moderate for scores

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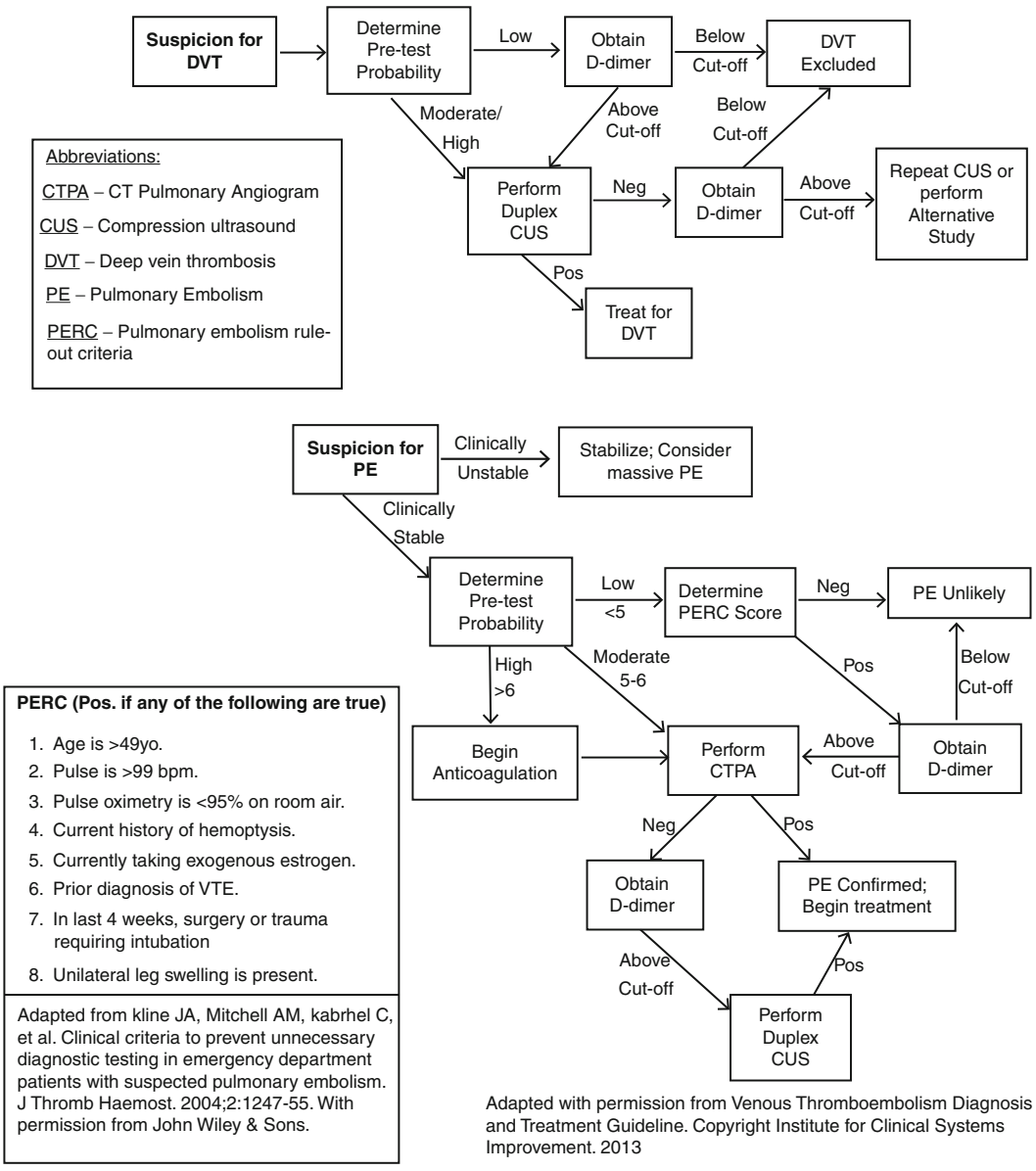
between 2 and 6, and high for scores greater than 6. Though some suggest a simple gestalt approach to pretest probability, determination based on experience is often inaccurate and should be used cautiously [10]. Pretest probability for DVT or PE, along with test availability and risk, should guide subsequent D-dimer and diagnostic imaging (see algorithm) [16].

Diagnostic Algorithms for DVT (Top) and PE (Bottom)



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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 [10]. Current assays are fast, readily available and highly sensitive (over 95 %) for VTE, but not nearly as specific [17]. False-positives can be seen in patients with malignancy, infection, recent surgery or trauma, and pregnancy [11]. It is worth noting that for patients 50 years or older, using an 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 [18].

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Compression ultrasound (CUS)

Widely available and noninvasive, CUS is the imaging procedure of choice for the diagnosis of DVT [14], with a sensitivity and specificity of 95 % and 98 % respectively when performed by a well-trained operator. 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 [11]. 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. Repeat CUS 1 week later is recommended for this group [11]. 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 [10].

Venography

Historically considered the gold-standard for DVT detection, venography involves injecting contrast into the venous system to assess for filling defects or collateral flow. Currently, venography is reserved for times when noninvasive tests cannot be performed or when noninvasive tests yield results counter to clinical suspicion [10]. 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 [19].

Computed Tomographic Pulmonary Angiography (CTPA)

Multidetector CT angiography has replaced conventional pulmonary angiography as the reference standard for diagnosing PE with high sensitivity and specificity up to 100 % and 97 %, respectively [16]. 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 [16]. Additionally, the PIOPED II trial showed that 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-1990s were achieved [19]. 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 [10, 20].

Ventilation-Perfusion (V/Q) Scanning

Ventilation-perfusion lung scans are reported as low, intermediate or high likelihood for presence of PE. A normal scan effectively excludes PE (negative predictive value of 100 %), [16] while high pretest probability and a high-probability V/Q scan has a positive predictive value of 96 % [21]. Up to 75 % of cases may result as nondiagnostic low or intermediate probability [21]. As with CTPA, results discordant with pretest probability require further work-up.

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 [10]. Those with normal angiography results have a 3-month VTE incidence less than 2 % with 0.3 % incidence of fatal PE [22]. More recent advances in V/Q Single-photon Emission CT (SPECT) have increased its sensitivity and specificity while limiting nondiagnostic results, which plague typical planar V/Q scans [23]. 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 [24]. Additionally, tests like a chest x-ray showing pleural infiltrates, or engorged central pulmonary artery vasculature with a

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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 [10].

Management

Management of VTE centers on initial stabilization of the patient, selection of anticoagulation therapy, and determining treatment duration. Providers may start pharmacological treatment in high risk patients (based on pretest probability) while undergoing testing, and delay treatment until testing is finished for low risk patients [13]. 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, 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 [25].

Initial Management

Given the variation of severity in presentations of patients with PE, the provider must ensure hemodynamic stability. For acute massive PE, sub-massive PE with significant right ventricular strain, or extensive acute proximal DVT, direct thrombolysis may be needed to dissolve the thrombus and reduce postthrombotic morbidity [25, 26]. Once the patient is stable, the treatment focus may be shifted toward anticoagulation, which is broadly the same in patients with PE or DVT. Goals of therapy include preventing clot propagation and possible PE (primary or subsequent) and minimizing complications. Resolution of a clot is not a direct goal of anticoagulation therapy [11, 25].

Initial anticoagulation can be accomplished with unfractionated heparin (UH), low-molecular weight heparin (LMWH), fondaparinux, apixaban, or rivaroxaban (see Table 3). UH has long been utilized in the initial treatment of VTE and when given intravenous (IV), is dosed via a nomogram based on periodic monitoring of the patient's activated partial thromboplastin time (aPTT) [28]. IV UH is preferred in the patient with PE who will likely be undergoing thrombolysis, those impaired subcutaneous absorption, or those with increased bleeding risk. 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 [13].

LMWH and fondaparinux have become the favored initial treatment for uncomplicated VTE. Both have equal efficacy, increased bioavailability, and less frequent dosing when compared to heparin [29]. Meanwhile, rivaroxaban and apixaban are new oral anticoagulants shown to have equivalent or better efficacy and safety as monotherapy for initial and long-term anticoagulation when compared to conventional therapy of LMWH and warfarin [30–32].

Outpatient 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. However, because of the need for an organized support system and time-of-day considerations for home care agencies, many patients may need hospitalization during the first 24 h to start therapy promptly [13].

Long-Term Anticoagulation

Initial anticoagulation should be initiated with long-term anticoagulation and continued for a minimum of 5 days and 24 h after the patient's international normalized ratio (INR) is above 2.0 (if treated with vitamin K antagonist (VKA) therapy). Bridging therapy via initial anticoagulation provides adequate anticoagulation while the vitamin K dependent clotting factors are depleted. The goal INR value for

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Table 3 Treatment table for venous thromboembolism (Compiled from Refs. [27, 28])

Parenteral anticoagulants							
Agent	Mechanism	Dosing	Half-life	Metabolism	Antidote	Monitoring	
Heparin	Binds antithrombin	IV: 80 u/kg bolus, then 18 u/kg.h SC: 333 U/kg, then 250 U/kg q12	90 min	Depolymerization	Protamine	aPTT (1.5-2.0x normal)	
LMWH[a] (Enoxaparin)	Binds antithrombin	1 mg/kg SC BID; 1.5 mg/kg SC daily if BMI <30	3–4 h	Depolymerization desulphation	Protamine	None required	
Fondaparinux[a]	Binds antithrombin	5.0 mg SC if <50 kg 7.5 mg SC if > 50 kg and <100 kg 10.0 mg if >100 kg	17–21 h	Insignificant	None	None required	
Oral anticoagulants							
Agent	Mechanism	Dosing	Half-life	Drug interactions[a]	Antidote	Monitoring	Parenteral anticoagulation
Vitamin K antagonist (warfarin)	Indirect thrombin inhibition	Initial dose of 5 mg–10 mg, changes based on INR	36 h	CYP2C9, CYP1A2, CYP3A4	Vitamin K	INR	Initially required, 5 days
Dabigatran[b]	Direct thrombin inhibitor	150 mg BID	14–17 h	P-glycoprotein inducers/ inhibitors	None	None required	Initially required, 5 days
Apixaban[b]	Factor Xa inhibitor	10 mg BID for 7 days, then 5 mg daily	8–12 h	CYP3A4/5. P-glycoprotein inducers/ inhibitors	None	None required	None required
Rivaroxaban[b]	Factor Xa inhibitor	15 mg BID for 3 weeks, then 20 mg daily or 15 mg daily if CrCl 15–50 mL/min	7–11 h	CYP3A4. CYP2J2 P-glycoprotein inducers/ inhibitors	None	None required	None required
Edoxaban[b]	Factor Xa inhibitor	30 mg or 60 mg daily	6–11 h	P-glycoprotein inducers/ inhibitors	None	None required	Initially required, 5 days

aPTT activated partial thromboplastin time, *BID* twice daily, *BMI* body mass index, *INR* international normalized ratio, *IV* intravenous, *SC* subcutaneous

[a]Not recommended in those with a creatinine clearance (*CrCl*) less than 30 mL/min

[b]Limited data in those with a creatinine clearance (*CrCl*) less than 30 mL/min

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treatment is 2.5, with an acceptable range of 2.0–3.0 [25]. Multiple trials have demonstrated the increased safety of starting long-term anticoagulation at the same time as initial anticoagulation [33, 34].

Warfarin, LMWH, oral and SC factor Xa inhibitors, and oral direct thrombin inhibitors provide long-term anticoagulation [35]. The most common and longest used agent is warfarin, a vitamin K antagonist. Warfarin is 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. Various tables and algorithms are available to guide warfarin dosing based on INR testing. One such validated protocol suggests monthly INR testing for patients in therapeutic range and weekly testing for those outside of their therapeutic range [36].

LMWH is also a viable option for long-term anticoagulation with similar efficacy and risk profile when compared to warfarin when used long-term [37]. LMWH is advantageous due to its ease of dosing, wide therapeutic window, no need for testing, 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 [13, 14]. Fondaparinux is a SC agent that is similar to LMWH and may also be used in long-term treatment [25].

Evidence for use of new oral agents suggests they are acceptable for long-term therapy [30–32, 38]. Recent meta-analyses have also shown lower bleeding risk compared to warfarin [39] and good tolerability in elderly patients [40]. However, because evidence for their use is not as strong as the previous agents, the clinician and patient must weigh the benefits (i.e., no monitoring) and risks (i.e., limited reversal) [13].

Length of Therapy

The standard length of anticoagulation therapy is at least 3–6 months. 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) [35]. Patients with an unprovoked proximal DVT of the leg or PE with low or moderate risk of bleeding in whom this is their first or second VTE, patients with VTE and active cancer, or those with genetic thrombophilias may require anticoagulation longer than 6 months [25, 35]. A 3 month duration should be considered in those with provoked VTE from a transient risk factor (i.e., trauma or immobilization) or those at higher risk for bleeding [35].

Additional Therapy

Daily low-dose aspirin (100 mg) after the initial anticoagulation treatment period may be considered. Pooled results of the recent randomized, multicenter WARFASA and ASPIRE trials showed a 32 % reduction in the rate of recurrence of VTE in patients receiving aspirin following anticoagulation therapy [41]. Use of compression stockings is recommended for 2 years in patients treated for symptomatic DVT to lessen risk for post-thrombotic syndrome [25]. Inferior vena cava filters (IVCs) are reserved for those with PE or proximal DVT and a contraindication to or a complication from anticoagulant treatment, or those with recurrent thromboembolism despite adequate anticoagulation [25].

Prevention

Recognizing those factors that increase one's risk for VTE is essential for prevention. Life-long anticoagulation may be appropriate for those with multiple risk factors. Chapter "► Athletic Injuries" discusses VTE prophylaxis for hospitalized and surgical patients in more detail.

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Superficial Thrombophlebitis

Superficial thrombophlebitis often coincides with VTE and risk factors include age over 60, male sex, existing infection, and existing bilateral thrombus [42]. Inflammation and pain along the course of a superficial vein are hallmarks of the condition. Duplex ultrasound is used to confirm the diagnosis as well as rule out associated thrombus. However, a patient who is low risk for DVT and whose thrombophlebitis is not in close proximity to the deep veins may not require ultrasound.

Treatment for thrombophlebitis consists of reduction of inflammation, effectively achieved with oral nonsteroidal anti-inflammatory drugs [43]. Anticoagulation is not standard treatment for thrombophlebitis and should only be initiated if the patient is at increased risk for VTE (venous segment >5 cm, inflammation ≤ 5 cm from the deep veins, medical risk factors).

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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 %. Therefore, the primary importance in diagnosing PAD lies in its role in identifying patients at risk for CAD morbidity and mortality.

Presentation and Diagnosis

Intermittent claudication, "defined as fatigue, discomfort, or pain that occurs in specific limb muscle groups during effort due to exercise-induced ischemia," is the presenting symptom in 10–35 % of patients. Atypical leg 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. Critical limb ischemia (CLI) includes chronic rest pain, ulcers, 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). Signs on physical exam include diminished pulses and bruits. Dependent rubor, early pallor when elevating the limb, reduced capillary refill, hair loss, and muscle wasting are signs of chronic ischemia. Acute limb ischemia may be accompanied by the 5 "Ps": pain, paralysis, paresthesias, pulselessness, and pallor. Arterial ulcerations are typically quite painful unless neuropathy is also present as can occur in diabetes.

A resting ankle-brachial index (ABI) in both legs is recommended for diagnosis of lower extremity PAD and should be reported as follows: normal 1.00 to 1.40, borderline 0.91 to 0.99, or abnormal 0.90 or lower [2]. A toe-brachial index should be used in patients with noncompressible vessels (defined as an ABI greater than 1.40). Further imaging is completed with duplex ultrasound and Doppler color flow (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). Where noninvasive techniques are inadequate and surgery is indicated, fluoroscopic angiography is the test of choice.

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, vascular inflammation, entrapment syndromes, or congenital abnormalities [1]. The differential considerations for claudication include neurogenic claudication (due to lumbar disk disease, spinal stenosis, or osteophytic changes), osteoarthritis, severe venous obstructive disease, chronic compartment syndrome, and shin splints (in younger persons).

Intervention

Atherosclerotic cardiovascular disease (ASCVD) risk factors, including hyperlipidemia, hypertension, and diabetes, should be managed according to current evidence-based guidelines [2]. 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. Supervised exercise training for a minimum of 30–45 minutes, three times per week for at least 12 weeks, improves intermittent claudication. Cilostazol (100 mg twice per day) is the first-line pharmacologic treatment for claudication in the absence of heart failure (HF). Pentoxifylline (400 mg three times per day) may be used as second-line therapy, but the benefits are likely small and not well established. Oral vasodilator prostaglandins, warfarin anticoagulation, vitamin E, and chelation should not be used to treat PAD. Surgical consultation 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 [3]. 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 [4]. 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.

Table 1 Etiologies of pericarditis

1. Infectious
a. Viral: Coxsackievirus, echovirus, Epstein-Barr virus, cytomegalovirus, adenovirus, parvovirus B19, human herpesvirus 6
b. Bacterial: Tuberculosis, *Coxiella burnetii*, rare other bacteria (pneumococcus, meningococcus, gonococcus, haemophilus, streptococcus, staphylococcus, chlamydia, mycoplasma, legionella, leptospira, listeria)
c. Fungal: Histoplasma (more likely in immunocompetent patients), aspergillus, *Blastomyces*, candida (more likely in immunosuppressed patients)
d. Parasitic: Echinococcus, toxoplasma (overall very rare)
2. Autoimmune
a. Pericardial injury syndromes: Post-myocardial infarction syndrome, post-pericardiotomy syndrome
b. Connective tissue diseases: Systemic lupus erythematosus, Sjögren syndrome, rheumatoid arthritis, systemic sclerosis, systemic vasculitides, Behçet's syndrome, sarcoidosis, amyloidosis
c. Autoimmune diseases: Familial Mediterranean fever, tumor necrosis factor receptor-associated periodic syndrome (TRAPS)
3. Neoplastic
a. Primary tumors: Pericardial mesothelioma (overall rare)
b. Secondary metastatic tumors: Lung cancer, breast cancer, lymphoma
4. Other
a. Trauma: Blunt chest trauma, penetrating thoracic injury, esophageal perforation, radiation
b. Metabolic: Uremia, myxedema (rare)
c. 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 2006 [5]

Presentation and Diagnosis

Patients typically present with chest pain. The pain is often sharp, severe, retrosternal, exacerbated with breathing, and relieved with sitting 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. These patients complain of 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 on 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 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. Within the last decade, colchicine (0.5 mg twice daily if weight >70 kg, once daily if weight <70 kg) has been studied for the treatment of acute pericarditis and found to be effective in decreasing 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.

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 2006

Adequate treatment of acute pericarditis is important in the prevention of 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 is constrictive pericarditis [3]. 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.

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 infectious endocarditis in the United States is estimated at between 3 and 10 cases per 100,000 patient-years, with a slight male predominance (68 %) and a median age of 58 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, is 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 account for 82–89 % of native valve endocarditis in both intravenous drug users (IVDUs) and non-IVDUs as well as non-valvular intracardiac device infections [7]. Fungal, protozoal, and gram-negative causes increase with prosthetic valve endocarditis (PVE) where gram-positive bacteria are responsible for 74 % of cases. The HACEK group (*Haemophilus* species, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*) occurs in 2 % of cases worldwide but only 0.3 % of cases within North America. BE caused by HACEK most commonly occurs in native valve, non-IVDUs. More than two-thirds of BE in IVDUs is due to *Staphylococcus aureus*. In addition, 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.

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 [7]. Fever, myalgias, fatigue, headache, and abdominal pain are common in all types of BE. HF 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 17 % of patients, while non-stroke embolization occurs in 23 % of cases. 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 3 sets of blood cultures from peripheral sites drawn at least 6 h apart from each other. At least 2, but preferably 3, sets of blood cultures separated by 30 min should be obtained from patients who present in severe sepsis or septic shock. A positive rheumatoid factor is present in only 5 % of cases, while an elevated ESR or CRP is present in approximately 60 % [7]. Other laboratory findings and imaging may reflect other complications as mentioned above. Serologies may be needed to determine the cause of infection when blood cultures are negative. ECG may reveal conduction abnormalities, indicating the extension of an aortic valve infection to a valve ring abscess, which carries a worse prognosis [6].

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 latter clinical 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 has been added to the major criteria definitions.

The Duke criteria have been extensively studied and found to have a sensitivity ranging from 75 % to 100 % 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 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.

Table 3 Definition of infective endocarditis according to the modified Duke criteria, with modifications shown in boldface

Definite infective endocarditis
Pathologic criteria
(1) Microorganisms demonstrated by culture or histologic examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen
(2) Pathologic lesions; vegetation or intracardiac abscess confirmed by histologic examination showing active endocarditis
Clinical criteria[a]
(1) 2 major criteria
(2) 1 major criterion and 3 minor criteria
(3) 5 minor criteria
Possible infective endocarditis
(1) 1 major criterion and 1 minor criterion
(2) 3 minor criteria
Rejected
(1) Firm alternate diagnosis explaining evidence of infective endocarditis
(2) Resolution of infective endocarditis syndrome with antibiotic therapy for ≤4 days
(3) No pathologic evidence of infective endocarditis at surgery or autopsy, with antibiotic therapy for ≤4 days
(4) Does not meet criteria for possible infective endocarditis, as above

[a]See Table 4 for definitions of major and minor criteria.
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

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

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
[a]Excludes single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis
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

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 obtained. The first day of therapy for determining the duration of antibiotics is the day when blood cultures were initially negative (if initial cultures

Table 5 Antibiotic regimens for native valve endocarditis

Viridans group streptococci and *Streptococcus bovis* (highly penicillin susceptible: MIC ≤0.12 μg/mL)
Penicillin G IV or ceftriaxone IV/IM for 4 weeks
[Penicillin G IV or ceftriaxone IV/IM] and gentamicin IV/IM for 2 weeks
Vancomycin IV for 4 weeks
Viridans group streptococci and *Streptococcus bovis* (relatively penicillin resistant: MIC >0.12 to ≤0.5 μg/mL)
[Penicillin G IV or ceftriaxone IV/IM] for 4 weeks and gentamicin IV/IM for 2 weeks
Vancomycin IV for 4 weeks
Viridans group streptococci and *Streptococcus bovis* (fully penicillin resistant: MIC >0.5 μg/mL)
Ampicillin IV and gentamicin IV/IM for 4 weeks (symptom duration ≤3 months)
Ampicillin IV and gentamicin IV/IM for 6 weeks (symptom duration >3 months)
Staphylococci (in the absence of prosthetic materials)
Oxacillin susceptible
[Nafcillin IV or Oxacillin IV] ± gentamicin IV/IM for 3–5 days
Cefazolin IV may replace nafcillin/oxacillin in patients with non-anaphylactic penicillin reactions
Penicillin G may replace nafcillin/oxacillin if MIC ≤0.1 μg/mL and does not produce β-lactamase
Vancomycin should be used in patients with immediate-type hypersensitive reactions to β-lactams
Oxacillin resistant
Vancomycin IV for 6 weeks
Enterococcus susceptible to penicillin, vancomycin, and gentamicin or streptomycin
Ampicillin IV for 4 weeks (symptom duration ≤3 months) or for 6 weeks (symptom duration >3 months)
Penicillin G IV and gentamicin IV/IM for 4 weeks (symptom duration ≤3 months)
Penicillin G IV and gentamicin IV/IM for 6 weeks (symptom duration >3 months)
Vancomycin IV and gentamicin IV/IM for 6 weeks
Streptomycin may replace gentamicin if isolate is sensitive to the former and resistant to the latter
Enterococcus resistant to penicillin but susceptible to aminoglycoside and vancomycin
β-lactamase-producing strain
Ampicillin-sulbactam IV and gentamicin IV/IM for 6 weeks (>6 weeks if gentamicin resistant)
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
E. faecium
Linezolid IV/PO for ≥8 weeks
Quinupristin-dalfopristin IV for ≥8 weeks
E. faecalis
Imipenem/cilastatin IV and ampicillin IV for ≥8 weeks
Ceftriaxone IV/IM and ampicillin IV for ≥8 weeks
HACEK group
Ceftriaxone IV/IM for 4 weeks (cefotaxime or another 3rd/4th generation cephalosporin may be used)
Ampicillin-sulbactam IV for 4 weeks
Ciprofloxacin IV/PO for 4 weeks (third-line treatment due to limited published in vivo evidence for IE)
Culture-negative endocarditis
Ampicillin-sulbactam IV and gentamicin IV/IM for 4–6 weeks
Vancomycin IV, gentamicin IV/IM, and ciprofloxacin IV/PO for 4–6 weeks
Bartonella
Suspected (culture negative)
Ceftriaxone IV/IM for 6 weeks and gentamicin IV/IM for 2 weeks ± doxycycline IV/PO for 6 weeks
Documented (culture positive)
Doxycycline IV/PO for 6 weeks and gentamicin IV/IM for 2 weeks
Rifampin IV/PO may replace gentamicin if the latter cannot be used

[a]The 2-week regimen is not appropriate for patients with known abscesses, impaired 8th cranial nerve function, creatinine clearance <20 mL/min, or infected with certain species.
Source: Baddour et al. 2005 [6]

Table 6 Antibiotic regimens for prosthetic valve endocarditis

Viridans group streptococci and *Streptococcus bovis* (penicillin susceptible: MIC ≤0.12 μg/mL)
[Penicillin G IV or ceftriaxone IV/IM] for 6 weeks ± gentamicin IV/IM for 2 weeks
Vancomycin IV for 6 weeks
Viridans group streptococci and *Streptococcus 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
Vancomycin IV for 6 weeks
Staphylococci
Oxacillin susceptible
[Nafcillin IV or oxacillin IV] plus rifampin IV/PO for ≥6 weeks and gentamicin IV/IM for 2 weeks
Cefazolin IV may replace nafcillin/oxacillin in patients with non-anaphylactic penicillin reactions
Penicillin G may replace nafcillin/oxacillin if MIC ≤0.1 μg/mL and does not produce β-lactamase
Vancomycin should be used in patients with immediate-type hypersensitive reactions to β-lactams
Oxacillin resistant
Vancomycin IV for ≥6 weeks plus rifampin IV/PO for ≥6 weeks and gentamicin IV/IM for 2 weeks
Enterococcus susceptible to penicillin, vancomycin, and gentamicin or streptomycin
Ampicillin IV for ≥6 weeks
Penicillin G IV and gentamicin IV/IM for ≥6 weeks
Vancomycin IV and gentamicin IV/IM for ≥6 weeks
Streptomycin may replace gentamicin if enterococcus isolate is sensitive to the former and resistant to the latter
Enterococcus resistant to penicillin but susceptible to aminoglycoside and vancomycin
β-lactamase-producing strain
Ampicillin-sulbactam IV and gentamicin IV/IM for 6 weeks (>6 weeks if gentamicin resistant)
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
E. faecium
Linezolid IV/PO for ≥8 weeks
Quinupristin-dalfopristin IV for ≥8 weeks
E. faecalis
Imipenem/cilastatin IV and ampicillin IV for ≥8 weeks
Ceftriaxone IV/IM and ampicillin IV for ≥8 weeks
HACEK group
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)
Culture-negative endocarditis
Early (≤1 year after surgery)
Vancomycin IV, cefepime IV, and rifampin IV/PO for 6 weeks plus gentamicin IV/IM for 2 weeks
Late (>1 year after surgery)
Ampicillin-sulbactam IV, gentamicin IV/IM, and rifampin IV/PO for 6 weeks
Vancomycin IV, gentamicin IV/IM, ciprofloxacin IV/PO, and rifampin IV/PO for 6 weeks
Bartonella
Suspected (culture negative)
Ceftriaxone IV/IM for 6 weeks and gentamicin IV/IM for 2 weeks ± doxycycline IV/PO for 6 weeks
Documented (culture positive)
Doxycycline IV/PO for 6 weeks and gentamicin IV/IM for 2 weeks
Rifampin IV/PO may replace gentamicin if the latter cannot be used

Source: Baddour et al. 2005 [6]

were positive). If a native valve is replaced during the initial course of antibiotics, US guidelines recommend changing to regimens recommended for PVE; however, European guidelines recommend continuation of native valve treatment. 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 counted days of native valve treatment can be subtracted from the total days needed for PVE 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 guideline-based treatments, 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 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 $\geq$3 sets of blood cultures drawn prior to starting antibiotics for a subsequent febrile illness.

Table 7 Indications for surgery in infectious endocarditis (IE)

Early surgery (before completion of antibiotics, during initial hospitalization)
Valve dysfunction causing symptoms of heart failure
Left-sided IE caused by *S. aureus*, fungal, 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 vegetations despite appropriate antibiotic therapy
Native valve endocarditis with mobile vegetations >10 mm in length
Complete removal of pacemaker or defibrillator with proven infection of pocket or leads
Surgery (variable timing)
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: Nishimura et al. 2014 [8]

Prevention

Prevention of IE in those with abnormal valvular architecture is covered in detail in chapter ▶ Medical Care of the Surgical Patient. In those with normal 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 non-genetic), 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 systolic (reduced ejection fraction) or diastolic (preserved ejection fraction) HF [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 antagonists, beta-blockers), invasive electrophysiology (cardiac resynchronization, implanted cardioverter defibrillator [ICD]), arrhythmia suppression (pharmacologic and non-pharmacologic), surgery (septal myomectomy, heart transplantation), and therapies targeted 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 1,400 autosomal dominant mutations have been identified in at least 8 genes that encode sarcomere proteins. 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 that 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 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 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. Twenty-four-hour electrocardiographic monitoring is recommended to identify patients who may be a candidate for an ICD, due to ventricular tachycardia, and also may 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.

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 guideline. 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. Dual-chamber pacing may be beneficial in patients >65 years of age; however, the benefits seen in younger patients appear to be due to a placebo effect.

In HCM patients with atrial fibrillation, anticoagulation with a vitamin K antagonist to an international normalized ratio (INR) of 2.0–3.0 is strongly recommended. The novel oral anticoagulants and aspirin have not been studied in patients with HCM. 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, while second-line agents include sotalol, dofetilide, and dronedarone. Radiofrequency ablation and surgical maze procedure 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 1,000–5,000, 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, endomyocardial biopsy, ECG, Holter, exercise stress) using major and minor factors. Modifications to the criteria for first-degree relatives of affected patients have been proposed to increase 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. Medical therapy with beta-blockers or amiodarone can be used in patients with hemodynamically stable VT, while an ICD should be considered in patients with a history of cardiac arrest, syncope, VF, or hemodynamically unstable VT.

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 prevalence in the United States averages 36/100,000 which results in 10,000 deaths per year. 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 [16]. HF caused by ASCVD, valvular heart disease, systemic hypertension, and congenital heart disease may also share the 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 [15]. 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, cardiac MRI 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 chapter ▶ Heart Failure.

Primary Restrictive Nonhypertrophied Cardiomyopathy (Mixed)

Diastolic dysfunction is the hallmark of the restrictive cardiomyopathy (RCM) phenotype; LV size, shape, and systolic function are either normal or nearly so [15]. 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 [15]. 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. Echocardiogram 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.

Treatment with diuretics is indicated for congestive symptoms and there may be a role for aldosterone antagonists, but caution must be exercised to avoid decreasing preload to the extent that cardiac output is further compromised. 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). Within the last 5 years, parvovirus B19 has eclipsed coxsackievirus as the most common etiology [18].

The inflammation of myocarditis is first caused by either direct microbial damage or toxic damage [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).

Table 8 Etiologies of myocarditis

1. Infection		
Bacteria	Staphylococcus, streptococcus, pneumococcus, meningococcus, gonococcus, salmonella, *Corynebacterium diphtheriae*, *Haemophilus influenza*, 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	
2. 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
3. Toxins		
Drugs	Amphetamines, anthracyclines, cocaine, cyclophosphamide, ethanol, fluorouracil, lithium, catecholamines, hemetine, interleukin 2, trastuzumab, clozapine	
Heavy metals	Copper, iron, lead	
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. 2013 [19], Cooper 2009 [18]

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. 2013 [19], Cooper 2009 [18]

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 increase mortality [18]. Exercise should be

avoided for several months. 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 ("Takotsubo") Cardiomyopathy (Acquired)

Stress cardiomyopathy, first described in Japan, is characterized by apical ballooning that 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, and the diagnosis is confirmed by the resolution of LV dysfunction 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 1,300–4,000 live births [20]. 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 normalized. Anticoagulation is particularly important due to a high rate of venous thromboembolism.

Tachycardia-Induced Cardiomyopathy (Acquired)

The severity of tachycardia-induced cardiomyopathy is correlated with the duration and rate of the inciting tachycardia [20]. 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 which were updated in 2013 (Table 10). All etiologies of PH are felt to 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

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. 2009 [22] and McLaughlin et al. 2009 [24]

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, 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, peripheral edema, hepatomegaly, and ascites.

If a patient has signs, symptoms, or history suggestive of PH, TTE is the next 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 focuses on 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 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 phosphodiesterase-5 inhibitors. 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 min. 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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Obstructive Airway Disease

Aarti Aggarwal and Chidinma Osineme

Contents

Chronic Cough

Cough is the often presenting feature of several non-life-threatening and life-threatening conditions, including obstructive airway disease. It is a vital reflex of the respiratory tract to clear the upper airways. Suppression of this reflex may lead to retention of airway secretions and respiratory infections [1]. A thorough medical history is important to denote whether a cough is acute (<3 weeks), subacute (3–8 weeks), or chronic (>8 weeks). This chapter will focus only on chronic cough.

Chronic cough can present difficulty in diagnosis and result in complications such as vomiting, rib fractures, urinary incontinence, syncope, muscle pain, fatigue, and depression [1]. The most common causes of chronic cough with normal chest radiograph in descending order, include upper airway cough syndrome (UACS) or formerly known as postnasal drip syndrome, chronic obstructive pulmonary disease (COPD), asthma and gastro-esophageal reflux disease (GERD), cigarette smoking or second hand exposure, and ACE-inhibitor use [1, 2]. These causes may occur alone or in combination. The diagnostic goal is to exclude serious conditions that present with chronic cough.

Cough is the primary feature of chronic cough. It is important to note the time of day the cough is most prominent, associated sputum production, as

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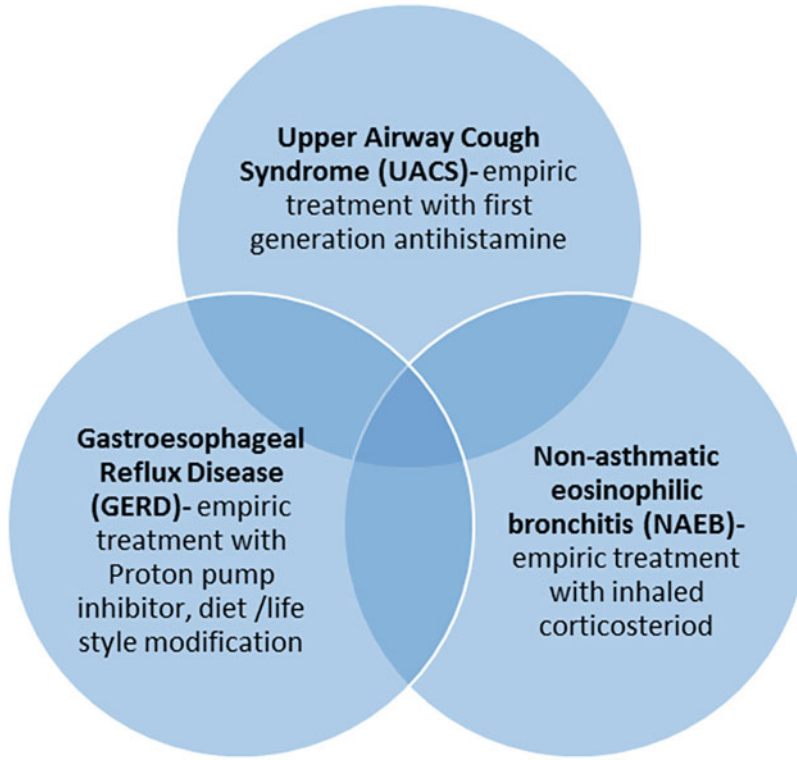

Fig. 1 Recommended management of chronic cough ≥15 years of age [2]

well as signs of drainage in the posterior pharynx, throat clearing, nasal discharge, cobblestone appearance of the oropharyngeal mucosa, and mucus in the oropharynx are relatively sensitive findings but are nonspecific for UACS [3]. If associated with heartburn, water brash, and belching and/or globus sensation most likely GERD is the cause. It is important to understand that cough alone can still be the only presenting feature of UACS, GERD, or cough variant asthma. Certainly, if the patient is taking an ACE-inhibitor, it may need to be discontinued as it is a possible cause of chronic cough.

After completion of a thorough history and physical examination, it may be helpful to obtain a chest radiograph and pulmonary function testing, bronchial provocation challenge, and sputum eosinophilia. Further investigation may be warranted and can include 24 h esophageal pH monitoring, upper endoscopy or video fluroscopic swallow evaluation, barium esophagram, sinus imaging, high resonance CT scan, bronchoscopy, echocardiogram, and environmental assessment [4].

Chronic cough can be multifactorial. If a patient has limited response to monotherapy, it is important to consider a treatment plan that addresses multiple etiologies. See Fig. 1.

Asthma

Asthma, one cause of ongoing cough, is a common respiratory disorder, characterized by periods of reversible airflow obstruction, inflammation, and hyperresponsiveness of the airways. Unfortunately, in the last 10 years, the number of persons with asthma in the USA has increased by 28 % [2]. Approximately, 39.5 million people, including 10.5 million children, in the USA have been affected by asthma. In 2010, asthma accounted for 3,404 deaths, 439,400 hospitalizations, 1.8 million emergency department (ED) visits, and 14.2 million physician office visits [5, 6].

Asthma exacerbations are triggered by multiple factors including exercise, airway infections, airborne allergens (e.g., pollen, mold, animal

Table 1 Commonly used FDA approved drugs for COPD

Drug name	Drug class	Delivery device	Usual adult dosage
Ipratropium (Atrovent)	Short-acting anticholinergic	MDI/ nebulizer	Two inhalations QID prn/500 mcg QID prn
Albuterol	SABA	MDI/ nebulizer	
Albuterol/Ipratropium (Combivent/duoneb)	Combined SABA and SAAC	MDI/ nebulizer	Two inhalations QID prn 2.5 mg/.5 mg QID prn
Salmeterol (Serevent Discus)	LABA	DPI	50 mcg BID
Tiotropium (Spiriva)	LAAC	DPI	18 mcg once/day
Aclidinium (Tudorza)	LAAC	DPI	400 mcg BID
Fluticasone/Salemeterol (Advair Diskus)	Combined ICS/LABA	DPI	250/50 mcg BID
Fluticasone/Vilanterol (BreoElipta)	Combined ICS/LABA	DPI	100/25 mcg once/day
Roflumilast (Dailiresp)	PDE-4 inhibitor	PO	500 mcg once/day

Source: Treatment guidelines from Medical Letter
MDI metered-dose inhaler, *DPI* dry powder inhaler
SABA short-acting beta agonist, *SAAC* short-acting anticholinergic
LABA long-acting beta agonist, *LAAC* long-acting anticholinergic
ICS inhaled corticosteroid, *PDE-4* phosphodiesterase inhibitor

dander, dust mites), occupational exposures, and air pollution (e.g., environmental tobacco smoke, particulate matter, and volatile organic compounds) [7, 8]. Although there is no cure, asthma can be controlled with appropriate medical therapies by avoidance of environmental exposures, particularly environmental exposures that may trigger an attack [7].

Common symptoms of asthma are wheezing, coughing, shortness of breath, and chest tightness or pain. Asthma attacks may be classified as mild, moderate, or severe enough to become life-threatening events [4]. The physical signs may be wheezing, rhonchi, or course breath sounds on auscultation. In addition, the patient may appear in respiratory distress with signs of accessory muscle usage, nasal flaring or grunting (in children), and altered mental status. Children may present will nocturnal cough only, while geriatric patients may present with chronic cough in absence of wheezing. In cases when wheezing occurs with exercise alone, the diagnosis of exercise-induced asthma (EIB) should be considered (Table 1).

Asthma is diagnosed on spirometry by observing a change in FEV_1 following bronchodilator administration. An increase of more than 12 % in patients 5–18 years of age, or more than 12 % and more than 200 mL in adults confirms the diagnosis of asthma. Although no single parameter has been identified to assess exacerbation severity, lung function is a useful method of assessment, with a PEF of 40 % or less of predicted function indicating a severe attack in patients 5 years or older [4].

If both the FEV_1/FVC ratio and the FVC are low, the patient has a mixed defect. Alternatively, a restrictive pattern is indicated by an FVC below the fifth percentile based on NHANES III data in adults, or less than 80 % in patients 5–18 years of age. If a restrictive pattern is detected, a consideration for pulmonary referral should be made for further evaluation and treatment.

Asthma exacerbation is defined as an increase in wheezing with or without hypoxia. If hypoxemia is present despite initial bronchodilator therapy, hospitalization should be considered. Management of asthma exacerbation is very similar to COPD exacerbation management with the exception of antibiotic therapy if no clear diagnosis of a bacterial infection is found. See Fig. 2.

In order to determine appropriate medical therapy, it is important to assess asthma severity. This can be done during an office visit by either

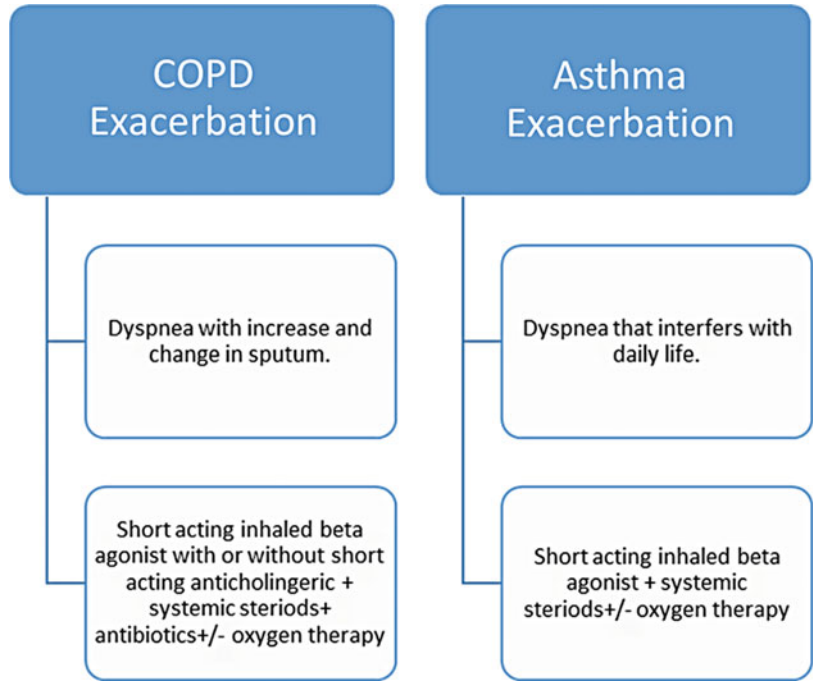

Fig. 2 Recommended treatment plan for asthma and COPD exacerbation

assessing symptoms through asthma assessment tools (ACT, ACQ, or ATAQ) or performing a peak expiratory flow (PEF) rate. There are well-validated questionnaires such as the asthma control test (ACT), asthma control questionnaire (ACQ), or asthma therapy assessment questionnaire (ATAQ) tools that can assist in assessment of asthma severity [4]. A PEF of 80 % or more of predicted or personal best categorizes patients' asthma as well controlled; however, less than 60 % of predicted or personal best indicates very poor control. Either technique has similar benefits in determining asthma control.

Asthma should be reassessed frequently if stepping up therapy or deescalating therapy.

The asthma severity determines the optimal initial therapy regimen (Tables 2 and 3). Close follow-up is warranted to reassess response to treatment and need for additional step up in therapy (Fig. 3). Treating more aggressively to obtain rapid control and then deescalating therapy to a maintenance regimen may be a more optimal approach. All patients regardless of severity should be provided a short-acting beta agonist. The use of a spacer with administration of metered-dose inhaler promotes drug distribution and effectiveness.

Arterial blood gas (ABG) is helpful in the inpatient setting when a patient has an exacerbation of asthma and is associated with moderate to severe hypoxia due to hypoventilation. If severe hypoxemia or hypercapnia is detected on ABG, it indicates the need for assisted ventilator support.

Certainly if avoidance is not helpful, there may be a role for antihistamines and nasal sprays. Consideration of a referral to an allergist may be helpful if allergy desensitization may be helpful for patients with severe asthma.

COPD

Often, the diagnosis of COPD is evident based on patient's history and physical examination alone. Any patient who has chronic dyspnea, cough, or sputum production along with a history of smoking exposure should be evaluated for COPD. However, pulmonary function test (PFT) is required to make a diagnosis of COPD [11]. Chronic obstructive pulmonary disease

Table 2 Stepwise approach for managing asthma for patients >12 years [9]

	Intermittent asthma	Persistent asthma (increasing severity of disease)				
		Mild ◄				► Severe
Preferred treatment	SABA as needed	Low-dose ICS	Low-dose ICS + LABA OR medium-dose ICS	Medium-dose ICS + LABA	High-dose ICS + LABA **AND** consider omalizumab for patients who have allergies	High-dose ICS + LABA + oral corticosteroid AND consider omalizumab for patients who have allergies
Alternative treatment		Cromolyn, LTRA, or theophylline	Low-dose ICS + either LTRA, theophylline or zileuton	Medium-dose ICS + either LTRA, theophylline or zileuton		
		Consider subcutaneous allergen immunotherapy for patients who have persistent, allergic asthma				

(COPD) is a major cause of morbidity and mortality in the USA and worldwide. Though it is one of the most preventable diseases, it affects more than 5 % of the US adults, and it is the third leading cause of death [9]. It is characterized by persistent airflow obstruction that is usually progressive and is not fully reversible. Cigarette smoking is the leading cause of COPD. However, long-term exposure to other irritants such as air pollution, chemical fumes, and household smoke can also contribute to COPD. Also, according to the WHO, passive smoking carries serious risks, especially for children and those chronically exposed [10]. The other rare cause of COPD is a genetic factor that causes deficiency of alpha-1 antitrypsin deficiency. If patient presents with COPD symptoms before the age of 40, consideration should be made to screen for alpha-1 antitrypsin deficiency.

The most common presenting symptoms of COPD include chronic cough, dyspnea that worsens on exertion, and chronic sputum production. COPD can remain unrecognized for number of years given its slowly progressive nature.

On physical examination, patients may have wheezing, decreased breath sounds on auscultation, or have completely normal exam. Since smoking is the most common cause of COPD, it is not uncommon that patients may appear older than stated age. During severe exacerbations, the patient may have labored breathing, appear altered in regards to mental status, and be acutely hypoxic.

Pulmonary Function Testing and Spirometry

Most helpful informations of the PFT are the forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), the FEV_1/FCV ratio, and the peak expiratory flow rate (PEFR). The postbronchodilator $FEV_1/FVC < 0.70$ or below the fifth percentile, based on data from the Third National Health and Nutrition Examination Survey (NHANES III) in adults, and less than 85 % in patients 5–18 years of age establishes the diagnosis. Severity of disease is further based on FEV_1 (Table 1 in chapter "► Population Based Health Care").

Patients should be routinely assessed in the clinic about their symptoms of COPD through the use of the COPD assessment test (CAT) and modified British Medical Research Council questionnaire (mMRC) score [12]. This helps to classify patients into four groups: group A (less symptoms, low risk), group B (more symptoms, less risk), group C (less symptoms, high risk), and group D (more symptoms, high risk) [11].

Laboratory and Imaging

Even though no lab is needed for diagnosis of COPD, different lab tests are sometimes ordered depending on the degree of suspicion for alternative diagnosis. For instance, CBC can be done for assessment of anemia as it can also present with dyspnea. Other labs that can be done depending on suspicion of other diagnosis may include

Table 3 Common FDA approved asthma controller medications for patients >12 years

Medication/formulations	Recommended dosing	Indications
Combined medication (inhaled corticosteroid + long-acting beta-2 agonist) Fluticasone/Salmeterol (Advair): DPI 100 mcg/50 mcg, 250 mcg/50 mcg, or 500 mcg/50 mcg MDI 45 mcg/21 mcg, 115 mcg/21 mcg, or 230 mcg/21 mcg	1 inhalation 2×/day; dose depends on level of severity or control	LABAs are used in combination with ICSs for long-term control and prevention of symptoms
Budesonide/Formoterol (Symbicort): MDI 80 mcg/4.5 mcg or 160 mcg/4.5 mcg	2 puffs 2×/day; dose depends on level of severity or control	
Mometasone/Formoterol (Dulera): MDI 100 mcg/5 mcg, 200 mcg/5 mcg	2 inhalations 2×/day; dose depends on severity of asthma	
Leukotriene Receptor Antagonists (LTRAs) Montelukast: (Singular) 4 mg or 5 mg chewable tablet, 4 mg granule packets, 10 mg tablet	10 mg every night at bedtime	Alternative therapy for treatment of patients with mild persistent asthma used as adjunctive therapy with ICSs, LTRAs can attenuate EIB. Monitor liver function
Leukotriene Modifiers Zafirlukast (Accolate): 10 mg or 20 mg tablet Take at least 1 h before or 2 h after a meal	40 mg daily (20 mg tablet 2×/day)	
5-Lipoxygenase Inhibitor Zileuton (Zyflo): 600 mg tablet	2,400 mg daily (give 1 tablet 4×/day)	
Immunomodulators Omalizumab (Xolair): Subcutaneous injection, 150 mg/1.2 mL following reconstitution with 1.4 mL sterile water for injection	150–375 mg subcutaneous every 2–4 weeks, depending on body weight and pretreatment serum IgE level	Adjunctive therapy for patients who have sensitivity to relevant allergens (e.g., dust mite, cockroach, cat, or dog). Monitor patients after injections; be prepared to treat anaphylaxis
Cromolyn (Intal) nebulizer: 20 mg/ampule	1 ampule 4×/day	They are used as alternative Medication They also can be used as preventive treatment before exercise or unavoidable exposure to known allergens
Methylxanthines Theophylline (Elixophyllin, Theo-24, Uniphyl): Liquids, sustained-release tablets, and capsules	Starting dose 10 mg/kg/day up to 300 mg maximum; usual maximum: 800 mg/day	Mild to moderate bronchodilator used as alternative, not preferred, or as adjunctive therapy with ICS. Theophylline may have mild anti-inflammatory effects. Monitoring of serum concentration is essential
Inhaled long-acting beta-2agonists (LABAs) Salmeterol (Serevent): DPI 50 mcg/blister	1 blister every 12 h	LABAs are not to be used as monotherapy for long-term control of asthma The preferred therapy to combine with ICS may be used before exercise to prevent EIB, but duration of action should not exceed 5 h with chronic, regular use

(*continued*)

Table 3 (continued)

Medication/formulations	Recommended dosing	Indications
Formoterol (Foradil Aerolizer): DPI 12 mcg/single-use capsule	1 capsule every 12 h	Anti-inflammatory medications that reduce airway hyperresponsiveness, inhibit inflammatory cell migration and activation, and block late phase reaction to allergen. Effective long-term control medication at all steps of care for persistent asthma. Reduce impairment and risk of exacerbations, but ICSs do not appear to alter the progression or underlying severity of the disease in children
Oral systemic corticosteroids Prednisone: 1, 2.5, 5, 10, 20, 50 mg tablets; 5 mg/cc, 5 mg/5 cc	40–60 mg/day as single or 2 divided doses for 3–10 days (1 mg/kg/day)	Used to gain prompt control of asthma during an acute exacerbation

Abbreviations: *DPI* dry powder inhaler, *IgE* immunoglobulin E, *MDI* metered-dose inhaler, *N/A* not available (not approved, no data available, or safety and efficacy not established for this age group) [10]

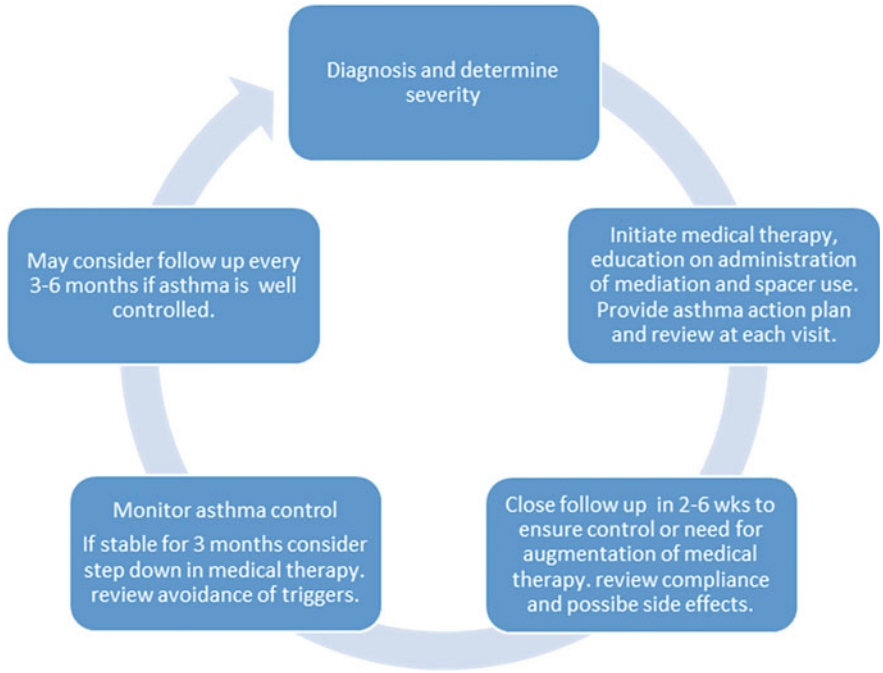

Fig. 3 Maintaining asthma control [9]

plasma BNP for heart failure and urea nitrogen/creatinine for underlying kidney disease. An elevated serum bicarbonate may indirectly suggest chronic hypercapnia [13]. Arterial blood gas (ABG) is helpful in the inpatient setting when a patient has an exacerbation of COPD and is associated with moderate to severe hypoxia due to hypoventilation. If severe hypoxemia or hypercapnia is detected on ABG, it indicates the need for assisted ventilator support.

Though chest radiography or any other imaging is not indicated in diagnosis of COPD, there

are a few radiographic features that suggest COPD such as: a flat diaphragmatic contour due to hyperinflation and increased retrosternal airspace on a lateral radiograph.

Special Testing

If a patient presents with symptoms of COPD and has persistent airflow obstruction prior to age of 40, especially in nonsmoker patient, testing for alpha-1 antitrypsin (AAT) should be considered. A serum level of AAT below 57 mg/dL is diagnostic [11].

Management

The approaches to management of both asthma and COPD are very similar and include avoidance, immunotherapy, exercise, pharmacological therapies, and psychological support.

COPD exacerbation can be defined as baseline change in patient's dyspnea, sputum quantity, and quality. Most of the exacerbations occur due to upper respiratory infection or air pollution, but one third can happen without any known cause [14]. Treatment for acute exacerbation includes consistent use of short-acting bronchodilators, antibiotics, and short course of oral prednisone [15, 16]. A recent study found that 5 days of oral prednisone use is noninferior to 14 days [17]. Oxygen supplementation may be needed depending on severity of symptoms and hypoxia. Interestingly, there is no evidence of superiority of nebulizer to MDI/spacer beta agonist delivery for home or emergency room setting [18].

COPD

For patients with intermittent symptoms, inhaled short-acting beta-2 agonists such as albuterol or/and anticholinergic inhaled medications such as ipratropium (Atrovent) can be used to relieve symptoms for acute episodes. When combined together, they provide additive response [19]. For patients with moderate to severe COPD, they should be on daily long-acting bronchodilators which can include beta-2 agonists like salmeterol (Severent) and/or long-acting anticholinergic such as tiotropium (Spiriva). One study has shown that when comparing tiotropium to salmeterol, it resulted in preventing exacerbations for longer period [19]. Often, when patient's symptoms are not well controlled with one class, these agents can be used together. Also, inhaled corticosteroids are approved in several combinations with long-acting beta-2 agonists. However, these can be considered when patients experience several COPD exacerbations. These are not approved to be used as monotherapy. Pneumonia is an important complication of treatment with inhaled corticosteroid-LABA products [19]. TORCH study has shown that it reduces exacerbation by 25 %; however, it does not slow progression of disease nor does it help to decrease mortality [20]. For patients with very severe COPD, consider starting triple therapy with a long-acting anticholinergic and a combined long-acting beta-2 agonist and corticosteroid. This may be warranted if symptoms persist despite dual medication therapy as it seems to reduce exacerbations and overall mortality [19].

Roflumilast (Daliresp) is an oral phosphodiesterase inhibitor which is indicated for patients with severe COPD associated with chronic bronchitis and history of several exacerbations [19]. Common side effects include nausea and diarrhea. Importantly, long-term oxygen therapy should be considered for patients with persistent hypoxemia of <88 % or PaO2 of 55 mmHg. See Table 3 for list of commonly used inhalers and their dosages.

Prevention of Exacerbations of Asthma and COPD

Climate

The interplay of climate and outdoor and indoor pollution on patients with asthma and COPD is very important. Extreme weather such as dry air of winter or humid air of the summer can impact the severity of both lung diseases. Often, staying indoors during times of extreme weather with

appropriate filtered air conditioning and heating system to maintain a constant climate indoors is vital.

Outdoor Air Pollution

Allergens that are more prominent during the four different seasons can easily cause exacerbations of lung disease. Attempts to avoid both manufactured and natural substances from tree, grass, plants, and molds can assist in control of pulmonary disease.

Indoor Air Pollution

Elimination of both personal and secondhand smoke exposure is very important in limiting factors for exacerbation. In addition, removing potential irritants from carpets, plants, air fresheners, and cleaning chemicals can reduce number of irritants in the indoor environment. Also, changing air filters of the heating and cooling unit monthly is just as important.

Immunization

An influenza vaccine is recommended yearly, October through March, for all asthma and COPD patients. Twenty-three valent pneumococcal vaccine should be offered to all the patients between the ages of 18 and 65 and second vaccination can be done 5 years from previous one or after the age of 65 whichever comes later [11].

Self-Management Education

Important topics which should be discussed include appropriate and proper use of their inhalers and spacer, early recognition of exacerbation symptoms, and perhaps discussion about advance directive [21, 22].

Exercise

Aerobic exercise is vital to improve exercise capacity, quality of life, and decrease health care utilization of patients with asthma and COPD [7]. Physical training lasting for at least 20–30 min, two to three times a week for at least 6 weeks, improves physical fitness in patients with asthma [7]. Pulmonary rehabilitation should be considered for patients who are more symptomatic (CAT $\geq$ 10 or mMRc $\geq$ 2) [7].

Special Populations

Pregnancy and Breastfeeding

The management of asthma does not change in the setting of pregnancy or breastfeeding. It is important to gain control early to prevent the risk of fetal hypoxia. Medications typically used to treat asthma do not confer any contraindication during pregnancy or lactation. Also, vaccination against pneumococcal and influenza during pregnancy is important.

Family and Community Issues

COPD is marked by gradual decline in health and increase in exacerbations over time. Respiratory failure, cardiovascular disease, and malignancy are major causes of death in patients with COPD. Hence, palliative care and hospice care are important components for patients with advanced COPD. Moreover, stepwise decline of quality of life may lead to isolation, depression, and anxiety. It is important to address emotional, family, and community support when caring for patients with COPD and severe asthma.

Prevention

Smoking cessation is a crucial step for all patients with COPD and asthma. It can reduce rate of decline in FEV1 and, hence, can help to slow the rate of progression of disease. It can be done through behavior counseling if patient is ready to quit. Other pharmacological interventions can be used including nicotine replacement therapy (nicotine patches, gum, and inhalers), bupropion (Wellbutrin), and varnicline (Chantix). Studies have shown that the combination of medical

therapy and counseling yields best results for smoking cessation [23].

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Pulmonary Infections

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Contents

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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]. In 2010, in the United States, pneumonia resulted in 1.1 million discharges from the hospital with an average length of stay of 5.2 days. Pneumonia accounted for 3.4 % of hospital deaths in 2006. In 2013 it accounted for 16.9 deaths per 100,000 population [2]. Pneumonia continues to be the leading killer of young children around the world, causing 14 % of all deaths in children ages 1 month to 5 years [3].

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. Hospital-acquired pneumonia is usually caused by more resistant bacteria such as *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Escherichia coli*. 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 [4]. The average yearly incidence of pneumonia, specifically community-acquired pneumonia, is 5–11 per 1000, with most incident cases occurring in the winter months [5]. 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, as well as history of previous hospital admissions or residence in a nursing facility. 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. Community-acquired pneumonia (CAP) must be distinguished from hospital-acquired pneumonia (HAP), healthcare-associated pneumonia (HCAP), or ventilator-associated pneumonia (VAP) before treatment is started. In addition, the cause of the pneumonia must be determined to be bacterial, viral, or atypical in nature before treating.

Bacterial pneumonia, specifically *Streptococcus pneumoniae*, is the most common cause of pneumonia across all ages [4]. Certain comorbidities or risk factors (see footnote of Table 1) such as age greater than 65, alcohol abuse, recent antibiotic use (within the past 3 months), coexisting medical

diagnoses of COPD or CHF, and exposure to day care/nursing home (child or adult) increase the likelihood that the patient may have illness caused by other bacterial causes or have a pneumonia that may require additional or different treatment [5].

In children, the suspected organism that has caused the pneumonia is based upon the age of the child: [5]

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*

In general, the same principles apply to adults in attempting to determine the most likely organism affecting the patient. The only difference is that organism and treatment options are not based on age, but on how ill the patient is, associated risk factors (see footnote of Table 1), and the location of treatment (outpatient vs. inpatient vs. intensive care unit (ICU)): [5]

Outpatient with no risk factors: *S. pneumoniae*, *M. pneumoniae* (esp. in the 18–30-year-old age group), *C. pneumonia*, *H. influenza*, respiratory viruses

Outpatient with risk factors: *S. pneumoniae*, *M. pneumoniae*, *C. pneumoniae*, mixed bacteria + virus or atypical, *H. influenzae*, *Legionella*, respiratory viruses and fungi

Inpatient, non-ICU: *S. pneumoniae*, *H. influenzae*, *M. pneumoniae*, *C. pneumoniae*, mixed bacteria + virus or atypical, respiratory viruses, *Legionella*, *Mycobacterium tuberculosis*, *Pneumocystis jirovecii*

Inpatient, requiring ICU admission: *S. pneumoniae (*including drug resistant), *Legionella*, *H. influenza*, gram-negative enteric organisms, *S. aureus*, *M. pneumoniae*, *Pseudomonas* sp., respiratory viruses, *C. pneumoniae*, *M. tuberculosis*, and fungi.

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.

Attention must be given to determining which of the following categories the patient falls into:

- ***Community-acquired pneumonia (CAP):*** Pneumonia that is not associated with hospitalization, healthcare/long-term care facility, or recent medical treatment or contact with the healthcare system [5].
- ***Healthcare-associated pneumonia (HCAP):*** Pneumonia that occurs in patients who have recently been hospitalized within the past 90 days, reside in a nursing home or long-term care facility, or have received parenteral antimicrobial therapy, chemotherapy, or wound care within the past 30 days [5].
- ***Hospital-acquired pneumonia (HAP):*** Pneumonia that occurs 48 h after admission to a hospital and was not present on admission. This infection is currently the second most common nosocomial infection in the United States and is associated with high mortality and morbidity [5].
- ***Ventilator-associated pneumonia (VAP):*** Pneumonia that occurs 48 h or more after being intubated [5].

Early recognition of risk factors for HCAP, HAP, or VAP with prompt empiric treatment with different antibiotic therapy than previously used is important in the prevention of significant morbidity and/or mortality associated with these illnesses [6, 7].

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.

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).

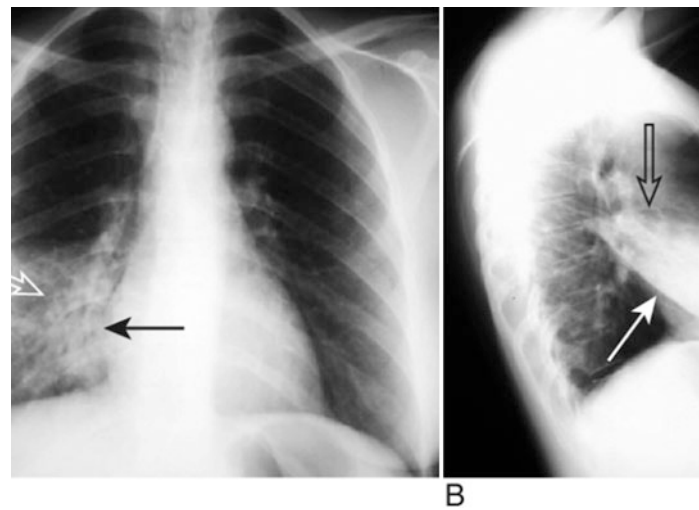

Fig. 1 X-ray of infiltrates in pneumonia [8].

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 evaluated for HAP, HCAP, or VAP, lower respiratory tract specimens should be cultured. These specimens can come from expectorated sputum or from a bronchoalveolar lavage (BAL) [7].

Special Testing

In patients presenting with severe CAP, special testing for urinary antigens of *Streptococcus pneumoniae* and *Legionella pneumoniae* serogroup 1 has been approved [9]. These tests provide a rapid result, with high specificity and sensitivity, thereby prompting targeted treatment.

Differential Diagnosis

The following might be considered in the differential based upon the patient's signs, symptoms, and comorbidities:

- Influenza
- Viral pneumonia
- Atypical pneumonia
- Acute bronchitis
- COPD exacerbation
- Congestive heart failure (CHF)
- Pleural effusion
- Pulmonary embolism

Treatment

Medications

The most important first determination to make in treatment for a patient with pneumonia is with regard to severity of illness; 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 [10].

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. According to the Infectious Disease 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 <4,000
- Thrombocytopenia, platelet count <150 k
- Temperature <36 °C
- Hypotension/septic shock requiring aggressive fluid hydration [10]

Location of treatment 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. Table 1 reviews the most likely organisms found in adults based on patient age and treatment location and provides the recommended empiric therapy with current dosing recommendations [5, 7, 9–11].

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 [10].

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.

Different antibiotic choices should be made for patients presenting with HCAP, HAP, or VAP. Multidrug-resistant pathogens must be considered with these infections and treated accordingly [7].

Patient Education

Decreasing a patient's chance of becoming ill with pneumonia is an important part of a primary care physician's job [12]:

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.

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 [4, 13]

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 [14]. It is usually transmitted from close person to person contact via respiratory droplets. The average incubation period is around 2–3 weeks [15], and infections tend to occur during the fall and winter.

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

Table 1 Target treatment, location, and organisms with empiric antibiotic recommendations

Age	Treatment location	Organisms being targeted	Antibiotic
<65, with no risk factors	**Outpatient**	*S. pneumoniae* *M. pneumoniae* *C. pneumoniae* *H. influenzae*	***Macrolide***: *Azithromycin*, 500 mg orally on day 1 and then 250 mg on days 2–5 *Clarithromycin*, 250 mg orally twice daily *Erythromycin*, 250 mg orally every 6 h or 500 mg orally every 12 h *Doxycycline*, 100 mg orally every 12 h for day 1 and then 100 mg orally daily
>65 +/− risk factors/ comorbidities[a]	**Outpatient**	*S. pneumoniae* *H. influenzae*	***Respiratory fluoroquinolone:*** *Levofloxacin (Levaquin)*, 500 mg orally every 24 h for 7–14 days or 750 mg orally every 24 h for 5 days *Moxifloxacin*, 400 mg orally daily *Gemifloxacin*, 320 mg orally daily ***B-lactam plus macrolide:*** *High-dose amoxicillin*, 1 g orally three times daily + macrolide (as dosed above) *Augmentin*, 2,000 mg orally every 12 h + macrolide (as dosed above) ***Alternatives to B-lactam include****:* *Cefuroxime, 500 mg twice daily* ***Alternative to macrolide****:* *Doxycycline, 100 mg orally twice daily*
All ages	**Inpatient, non-ICU**	*S. pneumoniae* *H. influenzae* *S. aureus*	***B-lactam plus macrolide:*** *Cefotaxime* (Claforan), 1–2 g IV/IM every 8 h + azithromycin 500 mg IV for 2 days and then followed by 500 mg orally daily (as dosed above) *Ceftriaxone* (Rocephin), 1–2 g IV/IM every 24 h, divided into two doses with max of 4 g/day + azithromycin (as dosed above) *Ampicillin*, 250–500 mg IV/IM every 6 h + azithromycin (as dosed above) ***Alternative to macrolide****:* *Doxycycline, 100 mg orally twice daily* ***Respiratory fluoroquinolone:*** *Levofloxacin (Levaquin)*, 500 mg orally every 24 h or 750 mg orally every 24 h *Moxifloxacin*, 400 mg orally daily *Gemifloxacin*, 320 mg orally daily
All ages	**Inpatient, ICU**	*S. pneumoniae* (including drug-resistant) *Legionella* *H. influenzae* Gram-negative enteric organisms	***B-lactam plus macrolide:*** Cefotaxime (Claforan), 1–2 g IV/IM every 8 h Ceftriaxone (Rocephin), 1–2 g IV/IM every 24 h, divided into two doses with max of 4 g/day Ampicillin-sulbactam (Unasyn), 250–500 mg IV/IM every 6 h **Plus:** Azithromycin 500 mg IV for 2 days, then followed by 500 mg orally every day *Levofloxacin (Levaquin)*, 750 IV every 24 h **Penicillin allergy: levofloxacin (as dosed above) + aztreonam 1–2 g IV every 8 h**

(*continued*)

Table 1 (continued)

Age	Treatment location	Organisms being targeted	Antibiotic
All ages	**Inpatient, ICU**	*Methicillin-resistant S. aureus (MRSA)*	**Above treatment for ICU patients plus:** *Vancomycin* 2 g IV daily divided every 6–12 h *Linezolid* (Zyvox) 600 mg IV or orally every 12 h
All ages	**Inpatient/ ICU**	*Pseudomonas aeruginosa*, suspected	**Antipneumococcal, anti-pseudomonal B-lactam:** Piperacillin-tazobactam (Zosyn) 3.375 mg IV every 6 h for 7–10 days Cefepime 1–2 g IV every 8–12 h for 10 days Imipenem 500 mg −1 g IV every 6 h **Plus, either** Ciprofloxacin 750 mg IV every 24 h Levofloxacin 750 mg IV every 24 h ***Penicillin allergy:*** ***Aztreonam 1–2 g IV every 6–8 h can be substituted for B-lactam***

From Mandell et al. [10]
[a]Risk factors and comorbidities
Chronic heart, lung, liver, or renal disease
Diabetes mellitus
Alcoholism
Malignancies
Asplenia
Immunosuppression or use of immunosuppressing drugs
Antimicrobial therapy within previous 3 months

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 an infiltrate and may be more prominent if the illness has been present for at least 2 weeks [15]. Cultures from throat, nasopharyngeal, or pleural fluid are considered the "gold standard" for diagnosis. 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) [14].

Treatment

Macrolides (erythromycin, azithromycin), tetracyclines (doxycycline), and fluoroquinolones (levofloxacin, moxifloxacin) are the typical therapies used to treat *M. pneumoniae*. Macrolides, particularly azithromycin, tend to be the most active against *M. pneumoniae* in in vitro studies [14]. The duration of antibiotic treatment is typically 5 days of azithromycin or 7–14 days with a tetracycline or fluoroquinolone.

Prevention

Use of appropriate hand hygiene and cough etiquette.

Chlamydial Infection

General Principles

Chlamydia is a 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* [16].

Approach to the Patient

Diagnosis

History and Physical

Along with other atypical pneumonias, patients can present with productive cough, sore throat [17], sinus congestion, and malaise.

Patients who have psittacosis, caused by *C. psittaci*, tend to have a history with exposure to infected birds. 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 [17]. A chest radiograph can reveal interstitial or lobar infiltrates [18]. As with *C. pneumoniae*, *C. psittaci* can be diagnosed with serologic testing.

Treatment

Doxycycline (100 mg orally twice daily) for 10–14 days is the treatment of choice for both *C. pneumoniae* and *C. psittaci*. Macrolides (azithromycin) can be used as well and are usually the choice for empiric treatment for atypical pneumonia [17, 18].

Prevention

Counsel patients about the importance of hand hygiene and cough etiquette [19].

Viral Pneumonia

General Principles

In immunocompetent adults with pneumonia, 18 % had a viral etiology and in 9 % a respiratory virus was the only pathogen identified. Studies that included outpatients found viral pneumonia rates as high as 36 % [10]. In children, viral etiologies for community-acquired pneumonia have been documented in up to 80 % of children younger than 2 years of age. Older children, ages 10–16, have a much lower percentage of viral pathogens [10].

Epidemiology

In immunocompetent adults, the most commonly seen virus is influenza and in children respiratory syncytial virus (RSV). Influenza affects 5–20 % of the US population annually, resulting in 226,000 hospitalizations and 36,000 deaths. RSV accounts for 25–40 % of pneumonia and bronchiolitis in infants [20].

Other common viruses are adenovirus and parainfluenza. Less common viruses include human metapneumovirus, herpes simplex virus, varicella-zoster virus, SARS-associated coronavirus, and measles virus [10].

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 [20].

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 [20].

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 [10].

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 examination 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) [10].

Table 2 Laboratory and imaging recommendations for viral pneumonia [22]

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

Treatment

Medications are given based on etiology of viral pneumonia. Influenza is treated with oseltamivir. 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 conditions, and RSV seasonality, palivizumab is available. This is a monoclonal antibody given in monthly intramuscular injections during RSV season [22].

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.

For influenza yearly 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 [20, 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 [23].

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 9,582 TB cases (or 3.0 per 100,000 persons) were reported in the United States in 2013 [24].

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 [23].

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 [25].

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 [23]. 40–50 % of TB cases are AFB smear-negative and 15–20 % have negative cultures [23]. 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 [23]. 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 regimens include isoniazid 900 mg and rifapentine 900 mg weekly for 3 months, rifampin 600 mg daily for 4 months, isoniazid 300 mg plus rifampin 600 mg daily for 3 months, or isoniazid 900 mg plus rifampin 600 mg twice weekly for 3 months. 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 [25].

Active TB is treated with a four-drug regimen: isoniazid, rifampin, ethambutol, and pyrazinamide for 2 months (intensive phase) followed by isoniazid and rifampin for 4 months (continuation phase). Pyridoxine supplementation is recommended to prevent isoniazid-induced neuropathy [25]. 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) [25].

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 [23].

Currently 17 % of newly diagnosed MTB cases are resistant to one or more first-line agents; isoniazid is the most commonly associated with resistance (10 %). There are strains resistant to both isoniazid and rifampin. In 2009 the World Health Organization estimated that 3.3 % of new TB cases were multidrug resistant [23].

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 μm 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 [19].

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 [27]. People 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 [27].

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 [28]. 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 completed.

Chest X-ray findings with acute pulmonary histoplasmosis include patchy or diffuse reticulonodular infiltrates; CT scans show +/− mediastinal or hilar lymphadenopathy [29]. 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 [28, 29].

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
- 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 [11, 28–30].

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

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.

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 [31]. The incidence of reported coccidioidomycosis has increased, from 5.3 per 100,000 population in 1998 to 42.6 per 100,000 in 2011 [32]. 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

Table 4 Treatment recommendations for histoplasmosis [28]

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

150,000 per year. It is also known as "valley fever" [33].

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 1–3 weeks after infection. The patient can present with respiratory complaints, fatigue, or arthralgia. 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 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 [34]. 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. The most common chest radiograph abnormality is airspace opacity (58 % of patients), followed by pulmonary nodules (22.8 %) and a cavitary lesion (13.2 %) [35].

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. 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 [19].

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 [36].

The bacteria, *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.

Epidemiology

Since being discovered, an estimated 8,000–18,000 people are hospitalized yearly in the United States with this infection [37]. 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 [36, 37]. 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 [37].

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 [10].

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 [4].

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 % [36, 37].

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 [30]. The time required for adequate testing using this method can take up to 3–8 weeks. Sensitivity and specificity of blood serum testing are 70–100 % and 100 %, respectively [36, 37].

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 [37]. The urinary antigen test yields a sensitivity and specificity of 80–90 % and >99 %, respectively [36, 37].

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 [4, 11, 37] (Table 5).

Immunizations and chemoprophylaxis

There are no vaccines available for prevention of *Legionella* infections.

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

Prevention

The most important factor in preventing infection is continued maintenance of water areas, such as hot tubs and heating/cooling water systems.

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, Epidemiology

Mycobacterium avium complex (MAC) is considered to be a non-tuberculous 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* [38].

Non-tuberculous 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 [38].

Patients who receive TNF-α blockers are susceptible to NTM infections and MAC was the most commonly implicated [39].

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 [40].

Laboratory and Imaging

Radiographic abnormalities are more specific and generally follow two distinct patterns. The first is bronchiectasis and nodular lesions mostly involving the lingual and middle lobe. The second is fibrocavitary lesions that mostly involve the upper lobes and resemble pulmonary tuberculosis [40].

Differential diagnoses for cavitary lesions include pulmonary malignancy, sarcoidosis, and infections by non-mycobacterial pathogens such as fungi and *Nocardia* species [40].

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 [39].

Pneumocystis Pneumonia

General Principles

Definition/Background, 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 [41]. Traditionally the nomenclature of the organism was *Pneumocystis carinii pneumonia* (***P. c****arinii* ***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 (***P****neumo****c****ystis* ***p***neumonia) to avoid confusion in medical literature [42]. 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 [43].

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. One may also see lung nodules. If the chest radiograph is normal, a high-resolution computed tomography (CT) scan may show ground-glass attenuation

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 [42].

Treatment

In not acutely ill patients with PCP (PaO2 > 70 mmHg), the treatment of choice is trimethoprim-sulfamethoxazole (TMP-SMX) 15–20 mg/kg PO daily in divided doses. 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 [14], trimethoprim (5 mg/kg orally three times daily) plus dapsone (100 mg orally daily) [44], or pentamidine 4 mg/kg intravenously daily. Glucose-6-phosphate dehydrogenase (G6PD) deficiency must be checked prior to using primaquine or dapsone [43]. 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 1,500 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 [41].

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Lung Cancer

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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. Between 2005 and 2009, a total of 1,054,393 new cases of lung cancer were diagnosed in the USA; it is estimated that in 2014, there will be 224,210 new cases of, and 159,260 deaths from, primary lung cancer [1]. Lung cancer also imposes a large financial burden on the healthcare system, with 2010 national expenditure for treatment totaling $12.12 billion [2].

However, over the 2005–2009 period, the overall incidence of lung cancer decreased, with a 2.6 % decrease in men and a 1.1 % decrease in women. The incidence and death rates decreased across most ethnicities and in both genders, with no subgroups experiencing an increase. Because cigarette smoking is the predominant risk factor for lung cancer [3], this decline may indicate not only a recent increase in smoking cessation rates but also a decrease in smoking initiation rates. By ethnicity, African-American men, compared to all men and women, have had the highest incidence and death rate over the last decade. Although the gap between African-American men and other men 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." Given that 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 cigarette use in the USA has been steadily decreasing: from 1965 to 2012, the percentage of current cigarette smokers decreased from 52 % to 24.8 % in adult men and 34 % to 19.3 % in adult women [5]. Among high school students, the overall prevalence has also been decreasing: from 1991 to 2011, the percentage of current cigarette smokers decreased from 27.6 % to 19.9 % in high school boys and 27.3 % to 16.1 % in high school girls. In 1997, the prevalence had peaked at 37.7 % in high school boys and 34.7 % in high school girls; it subsequently declined to current levels following the 1998 Tobacco Master Settlement Agreement, perhaps demonstrating the importance of public policy in curbing cigarette use among minors. 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. Smoking cessation will be covered in detail in another chapter.

Occupational and Environmental Exposure

It is estimated that occupational carcinogen exposures are responsible for 9–15 % of cases (approximately 20,000–34,000) of lung cancer in the USA [6]. 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 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) in the USA were attributable to radiation from CT scans [7]. Nonoccupational radon exposure is estimated by the EPA to have caused 21,100 deaths (13.4 % of all deaths) from lung

cancer in 2003. The EPA has also estimated 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 [8]. Additionally, a 2007 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. 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 [9]. 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 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) [10]. 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 [11].

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, breath) are only in developmental stages. Until recently, studies had not shown benefits from the imaging of high-risk patients. However, 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), the largest lung cancer screening trial to date, which enrolled over 53,000 patients in academic medical centers across the USA. The NLST demonstrated a 20 % reduction in lung cancer mortality compared to chest X-ray screening, with a number needed to treat of 320 [12]. Subsequent analyses estimate the expense of screening, once fully

implemented, to be approximately $81,000 per quality-adjusted life-year (QALY) gained [13], which is not dissimilar to the costs of screening mammography and colonoscopy. A large criticism of the trial is the possible lack of generalizability of the findings, namely, the participants were healthy volunteers, academic medical centers often have lower surgical complication rates and greater radiological expertise, and modern CT scanners are more advanced than those used in the trial. Also of concern is the inevitable large number of false-positive findings and the harms that would likely result from increased interventions. As of this writing, given the newness of this recommendation, the true benefits and costs have yet to be determined. Further subgroup analyses to identify higher risk groups may hone the recommended population to screen.

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) [14]. 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 [15].

The stage of disease is the strongest predictor of survival, though histology also plays an important part in prognosis [16]. 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 60 % for adenocarcinoma, 44 % for squamous cell, 41 % for large cell, and 20 % for small cell. For regional disease, the survival drops to 20 % for adenocarcinoma, 16 % for squamous cell, 16 % for large cell, and 11 % 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.

Table 1 Lung Cancer Type by Histology

Lung cancer type by histology [15]	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 for the numbers, the total may not add up to 100 %

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 on a chest X-ray or CT scan of the abdomen or chest obtained while working up another problem. Other common presentations are nonresolving 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 Eaton-Lambert 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 of these clinical scenarios. This complexity makes it beyond the scope of this chapter to make any detailed suggestions about workups for particular clinical presentations [17].

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. 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 [18].

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 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 [19] or the American College of Chest Physicians [20] 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 [21].

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 [16]. 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 [22, 23]. 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 tumor stage and pathology. Treatment decisions need to be worked out consensually between the patient and the treatment team of medical oncologists, radiation oncologists, and thoracic surgeons. The family physician can help to facilitate these decisions and advocate for the patient's values and preferences. Early stage disease is treated with surgery or possibly radiation therapy. More advanced stage disease is treated with various two chemotherapy drug combinations and possibly radiation therapy. Metastatic disease should undergo EGFR and ALK mutation testing for possible addition of a targeted monoclonal antibody agent [19].

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 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 [21].

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 [24].

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 [25–27].

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Selected Disorders of the Respiratory System

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Respiration and gas exchange require coordination between the chest wall, lungs, central nervous system, and pulmonary circulation. A disruption within any one of these systems or a change in the relationship between systems can result in impairments of ventilation, perfusion, or gas exchange. These disruptions can result in debilitating acute and chronic respiratory disorders. This chapter discusses the etiology, epidemiology, clinical presentation, diagnostic criteria, management, and notable public health implications of respiratory system disorders not addressed in prior chapters. Topic areas covered include acute respiratory distress syndrome (ARDS), pulmonary hypertension, pneumothorax, pleural effusion, interstitial lung disease, bronchiectasis, atelectasis, and pulmonary sarcoidosis.

Acute Respiratory Distress Syndrome

ARDS is a rapidly progressive pulmonary disorder occurring in medical or surgical patients. Approximately 190,000 cases of ARDS occur each year in the USA with the highest incidence in patients aged 75–84 years old. In the intensive care unit setting, approximately 10–15 % of admitted patients and upwards of 20 % of mechanically ventilated patients meet criteria for ARDS. The in-hospital mortality rate for ARDS is estimated at 34–55 % [1]. Population data suggest a trend towards improvement in survival for ARDS affected patients – an event thought to be driven by advancements in supportive care and mechanical ventilation. ARDS is characterized by a direct or indirect lung insult that results in the disruption of the alveolar-capillary barrier and stimulates the proliferation of inflammatory mediators. An increase in protein-rich interstitial fluid results in the loss of surfactant, thereby impairing gas exchange and decreasing pulmonary compliance. The majority of ARDS cases in adults can be attributed to sepsis, pneumonia, severe trauma, aspiration, and transfusion-associated lung injury. Risk factors in children are similar to those in adults, with the addition of age-specific disorders, including infection with respiratory syncytial virus and near drowning aspiration injury. Predictors of mortality in the patient with ARDS include severe hypoxemia, failure to improve oxygenation, pulmonary vascular dysfunction, severity of infection, and nontraumatic cause.

Diagnosis

The diagnosis of ARDS should be considered in any patient presenting with dyspnea, hypoxemia, and associated risk factors. A comprehensive evaluation including patient history, physical examination, laboratory testing, and imaging is essential to differentiate ARDS from similar respiratory conditions and to initiate appropriate therapy. The diagnostic criteria for ARDS, according to the 2012 Berlin definition [2], includes: (1) acute onset ($\leq$1 week of new or worsening respiratory symptoms), (2) presence of bilateral opacities on chest radiograph or computed tomographic scan, (3) exclusion of cardiac failure or fluid overload as the origin of pulmonary edema, and (4) impairment in oxygenation (characterized by 200 $<$ Pao_2/FIo_2 ratio $\leq$ 300 mmHg in mild ARDS; 100 $<$ Pao_2/FIo_2 ratio $\leq$ 200 mmHg in moderate ARDS; and Pao_2/FIo_2 ratio $\leq$ 100 mmHg in severe ARDS). Physical examination typically demonstrates evidence of respiratory distress, including tachypnea, tachycardia, and accessory muscle usage. It is important to distinguish ARDS from other conditions that result in acute hypoxemic respiratory failure with bilateral lung infiltrates, including pneumonia (viral or diffuse bacterial), cardiogenic pulmonary edema, acute inhalation injury, and malignancy (Table 1).

Management

The approach to medical support in patients with ARDS includes maintaining adequate oxygen delivery and providing comprehensive supportive care while minimizing ventilator associated lung injury (VALI) and secondary complications. The majority of affected patients will require sedation and mechanical ventilation in an intensive care setting. Treatment of reversible disease processes (e.g., infection) should accompany respiratory

Table 1 Differentiating ARDS from cardiogenic pulmonary edema and pneumonia

	ARDS	Cardiogenic pulmonary edema	Pneumonia
Review of systems			
Dyspnea	+	+	+
Pleurisy	+/–	–	+
Sputum production	+/–	–	+
Physical examination findings			
Tachypnea	+	+	+
Hypoxemia	+	+	+
Fever	+/–	–	+
Jugular venous distension	–	+	–
S3 or S4 gallop	–	+	–
Pulmonary rales	+	+	+
Peripheral edema	–	+	–
Diagnostic testing			
Bilateral infiltrates on CXR	+	+/–	+/–
Focal infiltrate on CXR	–	–	+
Cardiomegaly on CXR	–	+	–
Elevated BNP[a]	–	+	–
Pao2/FIo2 ratio $\leq$ 200 mmHg	+	–	–
Response to therapy			
Antibiotic therapy	–	–	+
Diuretic therapy	–	+	–
Supplemental oxygen	–	+	+

[a]Brain natriuretic peptide level
+ present, – absent, +/– can be either present or absent

support efforts. Considerations in mechanical ventilation include: (1) low tidal volume ventilation, or lung protective ventilation, which has been shown to improve mortality by reducing VALI and decreasing inflammatory mediator release, (2) titration of positive end-expiratory pressure (PEEP) levels to recruit atelectatic, undamaged alveoli [3], and (3) permissive hypercapnia to minimize VALI due to alveolar over distension. A subpopulation meta-analysis of 11 randomized controlled trials suggests that prone positioning during mechanical ventilation is associated with improved survival, although patient selection should be reserved for severely ill persons failing to improve with low tidal volume ventilation strategies [4]. A spontaneous breathing trial is indicated in the patient who is hemodynamically stable and able to maintain oxygen requirements through noninvasive methods.

Supportive care in ARDS includes the appropriate balance of sedation, analgesia, and neuromuscular blocking agents; nutritional support and management of blood glucose; minimizing nosocomial infections (e.g., catheter associated urinary tract infections and ventilator associated pneumonia); stress ulcer prophylaxis (omeprazole 40 mg orally, intravenously, or via nasogastric tube daily; ranitidine 150 mg orally or via nasogastric tube two times daily or 50 mg intravenously every 6–8 h; sucralfate 1 g orally or via nasogastric tube four times daily) and deep venous thrombosis prophylaxis unless medically contraindicated (enoxaparin 40 mg subcutaneously daily; unfractionated heparin 5,000 units subcutaneously two times daily). While a definitive role for glucocorticoid therapy in the treatment of ARDS has not yet been established, early initiation of corticosteroid therapy may be associated with an increase in ventilator free days [5].

Prevention

A review of current literature and population based studies suggests that potentially preventable hospital exposures contribute to the development of hospital-acquired ARDS in at-risk patients. These exposures include preventable medical and surgical adverse events, inadequate empiric antimicrobial therapy, large volume blood product transfusion, large volume intravenous fluid administration, and documented pulmonary aspiration. Quality improvement efforts to mitigate these exposures may aid in the reduction of hospital-acquired ARDS and improve safety outcomes for critically ill patients [6].

Family and Community Issues

The family physician is essential in coordination of posthospital care for survivors of ARDS. This population is at heightened risk for long-term functional impairments (exercise limitation, decreased physical quality of life) as well as psychological sequelae (depression and anxiety, social isolation) and increased utilization of health care services [7].

Pulmonary Hypertension

Pulmonary hypertension is a progressive disease of the pulmonary circulation defined by a mean pulmonary arterial pressure $\geq$ 25 mmHg at rest measured by right heart catheterization. The condition affects all age groups, both men and women equally. Due to the broad classification system and numerous etiologies for pulmonary hypertension, epidemiological data is limited. Mortality is estimated at 5.4 per 100,000 persons with women and African-American persons adversely affected. Pulmonary hypertension is characterized by one of the following: (1) primary elevation in the pressure of the pulmonary arterial system (pulmonary arterial hypertension) or (2) a secondary elevation in the pressure of the pulmonary venous and pulmonary capillary systems (pulmonary venous hypertension). Pulmonary hypertension can present at any age from infancy to adulthood, although pediatric populations are more frequently diagnosed with pulmonary arterial hypertension due to congenital heart disease or idiopathic etiologies.

Classification

In 1998, the World Health Organization (WHO) sponsored a symposium on primary pulmonary hypertension, from which a new classification system for the disease was developed. Classification of pulmonary hypertension is essential in estimating prognosis and initiating therapy. This classification has undergone minor modifications, with the most recent occurring during the fourth World Symposium on Pulmonary Hypertension (Dana Point, 2008); this classification divides pulmonary hypertension into five categories based on commonalities in pathophysiologic mechanism of disease, clinical presentation, and therapeutic approaches [8]. These five categories include: (1) pulmonary arterial hypertension, (2) pulmonary hypertension owing to left heart disease, (3) pulmonary hypertension owing to lung diseases and/or hypoxia, (4) chronic thromboembolic pulmonary hypertension, and (5) pulmonary hypertension with unclear multifactorial mechanisms. Further breakdown within classes can be reviewed in Table 2.

Diagnosis

A comprehensive evaluation is indicated in all patients with suspected pulmonary hypertension, including patient history, physical examination, laboratory testing, and imaging. Patients most commonly present with dyspnea on exertion and fatigue. As the disease progresses, chest pain, dizziness, cough, syncope, hemoptysis, ascites, and edema may develop. A thorough review of systems should be performed to identify symptoms suggestive of associated and underlying conditions. It is important to distinguish pulmonary hypertension from other causes of exertional dyspnea. The differential diagnosis must include

Table 2 Classification of pulmonary hypertension

1. Pulmonary arterial hypertension (PAH)
1.1 Idiopathic
1.2 Heritable
1.2.1 BMPR2
1.2.2 ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)
1.2.3 Unknown
1.3 Drug- and toxin-induced
1.4 Associated with:
1.4.1 Connective tissue diseases
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart diseases
1.4.5 Schistosomiasis
1.4.6 Chronic hemolytic anemia
1.5 Persistent pulmonary hypertension of the newborn
1'. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
2. Pulmonary hypertension owing to left heart disease
2.1 Systolic dysfunction
2.2 Diastolic dysfunction
2.3 Valvular disease
3. Pulmonary hypertension owing to lung diseases and/or hypoxia
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental abnormalities
4. Chronic thromboembolic pulmonary hypertension
5. Pulmonary hypertension with unclear multifactorial mechanisms
5.1 Hematologic disorders: myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

ALK1 activin receptor-like kinase type 1
BMPR2 bone morphogenetic protein receptor type 2
HIV human immunodeficiency virus
Source: Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. Journal of the American College of Cardiology 2013; 62(25 Suppl):D34–41, with permission

coronary artery disease, left-sided heart failure, acute and chronic liver disease, and Budd-Chiari syndrome.

Physical findings arise from compensatory changes in the right ventricle. Common examination findings in early disease include a prominent second heart sound (loud P_2 heard best in the left upper sternal border), systolic murmur of tricuspid regurgitation, increased jugular venous pressure (neck vein distension), ascites, or peripheral edema. The clinician should tailor the physical examination based upon the suspected classification of pulmonary hypertension. Laboratory testing should be ordered based on suspicion of underlying disease and may include a complete blood count with differential, liver function test, brain natriuretic peptide, thyroid studies, antinuclear antibody (ANA), HIV serology, rheumatoid factor (RF), and antineutrophil cytoplasmic antibody (ANCA) [9].

Chest radiography of the patient with pulmonary hypertension classically reveals prominent interstitial pulmonary markings and attenuated peripheral pulmonary arteries. Enlargement of the right ventricle and right atrium and evidence of underlying pulmonary disease (e.g., pulmonary fibrosis) may also be noted. Changes on electrocardiogram do not correlate with disease severity or prognosis but may aid in detecting right ventricular disease. Signs of right ventricular hypertrophy or strain on electrocardiogram may include right axis deviation, incomplete or complete right bundle branch block, increased P wave amplitude in lead II, and R wave/S wave ratio > 1 in lead V1. The transthoracic echocardiogram is useful in the estimation of pulmonary artery systolic pressure and the assessment of right ventricular size, thickness, and function. Evidence of congenital heart disease and the status of the heart valves and septum can also be determined by the echocardiogram. Pulmonary function testing, including lung volumes, diffusion capacity, and spirometry, may aid in characterizing underlying lung disease such as emphysema or pulmonary fibrosis. A six minute walk test can be useful in establishing baseline function, estimating prognosis, and monitoring clinical response to treatment. This involves exercise oximetry during a timed six

Table 3 Treatment of underlying conditions associated with pulmonary hypertension

Category	Treatment goal	Intervention
Pulmonary arterial hypertension	Reduce vascular resistance, endothelial and smooth muscle dysfunction	Advanced therapy strategies
Pulmonary hypertension due to left heart	Reduce left atrial pressure to decrease PAP	Afterload reduction Diuretics
Pulmonary hypertension due to disorders of the respiratory system and/or hypoxemia	Maximize pulmonary function and correct hypoxemia	Continuous oxygen therapy Glucocorticoids Bronchodilators Nocturnal CPAP
Chronic thromboembolic pulmonary hypertension	Restore luminal patency and reduce vascular resistance	Lifelong anticoagulation Vena cava filter Surgical thromboendarterectomy
Pulmonary arterial disease related to infection, inflammatory conditions, or toxins	Reduce vascular resistance, endothelial and smooth muscle dysfunction	Disease modifying antiinflammatory agents Antiinfectious agents Avoiding toxin or causative drugs

PAP positive airway pressure, *CPAP* continuous positive airway pressure

minute walk. Polysomnography may be appropriate if sleep-disordered breathing (e.g., obstructive sleep apnea) is suspected. A ventilation-perfusion (V/Q) scan is the preferred imaging study to evaluate patients for chronic thromboembolic pulmonary hypertension.

Due to the need for cardiac catheterization to confirm the diagnosis of pulmonary hypertension, early cardiology consultation is indicated. The right heart catheterization is indicated to confirm the diagnosis, determine disease severity, and establish therapeutic intervention.

Management

Prognosis amongst patients with pulmonary hypertension is highly variable and depends on both the classification and severity of disease. Untreated, pulmonary hypertension is a progressive disease that can be fatal. An approach to more goal-directed management of pulmonary hypertension may improve long-term outcomes in patients. Such treatment goals, according to the American College of Cardiology, include: (1) modified New York Heart Association functional class I or II, (2) six-minute walk distance $\geq$ 380–440 m, (3) cardiopulmonary exercise test-measured peak oxygen consumption $>$ 15 ml/min/kg and ventilatory equivalent for carbon dioxide $<$ 45 l/min/l/min, (4) brain natriuretic peptide level near normal range, (5) echocardiograph and/or cardiac magnetic resonance imaging demonstrating normal or near-normal right ventricular size and function, and (6) normalization of right ventricular function with right atrial pressure $<$ 8 mmHg and cardiac index $>$ 2.5–3.0 l/min/m^2 [10].

Treatment begins with therapy targeted to any underlying condition (Table 3). Supplemental oxygen, diuretics, anticoagulation, and digoxin therapy should be considered as primary treatment strategies in all patients with pulmonary hypertension. Advanced therapy should be considered in WHO functional class II, III, or IV patients and may include prostanoids, endothelin receptor antagonists, phosphodiesterase 5 inhibitors, soluble guanylate cyclase stimulants, or calcium channel blockers to reduce right ventricular overload based on right heart catheterization findings [11]. Emerging therapies in the treatment of pulmonary hypertension include antiproliferative strategies, transcription factor-based therapy, immune cell-focused approaches, and epigenetic

modulation-based therapy [12]. Patients with idiopathic pulmonary arterial hypertension may be candidates for lung transplantation. Maintenance of updated influenza and pneumococcal vaccinations is recommended.

Pneumothorax

A pneumothorax is defined as the presence of gas within the pleural space and can be classified by etiology as spontaneous or acquired (iatrogenic or traumatic). The spontaneous pneumothorax can further be categorized as primary (no known underlying pulmonary disease) or secondary (known underlying pulmonary disease). The gas may enter through the chest wall and parietal pleura due to trauma or may originate from gas-filled gastrointestinal structures such as a ruptured esophagus or bowel with subsequent escape of gas across the diaphragm from a pneumoperitoneum. Most often the gas originates in the lung with leakage following alveolar or tracheobronchial injury or through the visceral pleura due to focal pulmonary processes.

Primary Spontaneous Pneumothorax

In primary spontaneous pneumothorax (PSP), the pneumothorax results from the rupture of a subpleural bleb, typically in persons with no prior lung disease. The incidence is 7.4 cases per 100,000 in men and 1.2 per 100,000 in women and peaks in persons between 20 and 30 years of age [13]. Risk factors for the development of PSP include cigarette smoking, family history of primary spontaneous pneumothorax, Marfan syndrome, and homocystinuria.

Diagnosis

The most common symptoms of PSP include sudden onset of pleuritic chest pain and dyspnea. The chest pain may be dramatic and severe, localized over the area of pneumothorax and sometimes radiating to the ipsilateral shoulder. The severity of symptoms may be related to the volume of air within the pleural space. Physical examination often reveals a mild tachycardia. Auscultation reveals diminished breath sounds and decreased chest excursion on the affected side. Chest percussion reveals hyperresonance over the affected side. Arterial blood gases may reveal hypoxemia without hypercapnia due to ventilation-perfusion mismatch in otherwise healthy lung tissue.

The chest radiograph in PSP is diagnostic, demonstrating a lucent area of pleural space devoid of the normal vascular markings that divide the edge of the lung from the chest wall [14]. While it is difficult to estimate the size of the pneumothorax by chest radiograph, a 1-in. lucent rim corresponds approximately to a 30 % collapse of the lung. In critically ill patients unable to remain upright, a supine chest radiograph will reveal lucency in the costophrenic sulcus rather than the apex.

Management

Management strategies in PSP are directed at lung reexpansion (removal of air in the pleural space), symptomatic management, and prevention of recurrence. Treatment options depend on the size of the pneumothorax and the severity of symptoms. Small pneumothoraces involving less than 15 % of the hemithorax (<3 cm between the lung and chest wall on chest radiograph) may resolve without therapy, provided no additional leakage occurs. Complete resolution is expected within 10 days. Supplemental oxygen can facilitate resolution by increasing the pressure gradient of nitrogen from the pleural space into the capillaries and facilitating resorption of the pleural air. In uncomplicated cases of PSP, both manual aspiration and small-bore catheter insertion with Heimlich valve are cost-effective and minimally invasive interventions with comparable success rates and shorter hospitalizations as compared to tube thoracostomy [15, 16]. A large pneumothorax or a patient with severe symptoms is associated with increased likelihood of failure of simple aspiration [17] and will likely require chest tube insertion to permit reexpansion of the lung. Video-assisted thoracoscopic surgery pleurodesis, chemical pleurodesis, or thoracotomy should be considered after two ipsilateral PSPs or when a

5- to 7-day course of chest tube therapy fails to result in lung reexpansion. The recurrence rate for PSP is approximated at 30 % and does not appear affected by treatment choice [13].

Family and Community Issues

The strong association between cigarette smoking and rates of PSP provides an opportunity for the family physician to coordinate smoking cessation interventions with a goal to prevent recurrent pneumothoraces.

Secondary Spontaneous Pneumothorax

In secondary spontaneous pneumothorax (SSP), the pneumothorax results from the rupture of a subpleural bleb as a complication of underlying lung disease. The incidence is 6.3 cases per 100,000 in men and 2 per 100,000 in women with peak incidence highest among persons over 55 years of age [13]. While most pulmonary diseases can result in an SSP, the finding is most frequently associated with pulmonary infection (*Pneumocystis jiroveci* pneumonia, Mycobacterium tuberculosis, necrotizing pneumonia), interstitial lung disease, primary or metastatic lung malignancy, cystic fibrosis, and COPD. The pathophysiology of SSP remains unclear. It is thought that air enters the pleural space following alveolar rupture due to a mechanism associated with the underlying lung disease.

Diagnosis

Symptoms, physical examination, and radiographic findings in SSP are similar to those of PSP with several exceptions. Symptoms in SSP can be more severe due to the diminished pulmonary reserve associated with chronic underlying pulmonary disease. Imaging in SSP may require computed tomography of the chest in addition to chest radiograph in order to definitively determine the size and location of pleural air.

Management

Management strategies in SSP mimic those of PSP and are directed at lung reexpansion (removal of air in the pleural space), symptomatic management, and prevention of recurrence. Unlike PSP, the majority of patients presenting with SSP will require hospitalization and pleural drainage due to the severity of underlying lung disease and risk of adverse outcomes. Patients predisposed to hypercapnia due to chronic pulmonary disease (e.g., COPD) may require higher concentrations of supplemental oxygen. Recurrence rates for SSP range from 40 % to 56 % and frequently occur within the first 6 months after the first episode. Due to the marked rate of recurrence, thoracotomy, video-assisted thoracoscopic surgery, or chemical pleurodesis should be performed in all patients undergoing treatment for an initial SSP.

Tension Pneumothorax

A tension pneumothorax can result from either a spontaneous or a traumatic pneumothorax and is a life-threatening emergency. Tension develops as air freely enters the pleural space during inspiration but is unable to escape during expiration. The result of this one-way valve is further lung collapse with shifting of the trachea and mediastinum away from the pneumothorax. Patients with a tension pneumothorax are in acute respiratory distress and have dilated neck veins, tracheal deviation, and absence of breath sounds on the affected side. Patients are in danger of impending cardiovascular collapse unless prompt treatment ensues. Immediate insertion of a large-bore needle (16 gauge) into the affected pleural cavity at the second intercostal space releases the trapped air, relieves the pressure, and results in rapid improvement in cardiac output and blood pressure [14].

Pleural Effusion

Pleural effusions are an accumulation of fluid in the pleural space resulting from a disparity between pleural fluid formation and resorption. Typically, oncotic and hydrostatic pressures regulate this fluid movement; however, decreased capillary oncotic pressure or elevated capillary and interstitial hydrostatic pressures may lead to

Table 4 Pleural fluid characteristics based on light's criteria rule [20]

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	< Two thirds of upper limit of normal serum LDH	> Two thirds of upper limit of normal serum LDH
pH	>7.40	<7.40
WBC count	Typically < 1,000/μL	Typically > 1,000/μL

LDH lactate dehydrogenase, *WBC* white blood cell

accumulation of fluid. Pleural effusions are caused by more than 50 disease processes with congestive heart failure, cirrhosis with ascites, pleuropulmonary infections, malignancy, pulmonary embolism, and pancreatitis accounting for more than 90 % of all cases.

Diagnosis

A comprehensive evaluation, including patient history, physical examination, and thoracentesis to sample and analyze the pleural fluid, aids the physician in establishing the etiology of a pleural effusion. Symptoms of pleural effusions are the result of pleural inflammation or mechanical effects of the fluid volume. The most common presenting complaints include pleuritic chest pain, dyspnea, nonproductive cough, and fever. Pain may be referred to the abdomen or ipsilateral shoulder. Patients may be asymptomatic. The pulmonary examination characteristically reveals decreased breath sounds over the area of the effusion. Tactile fremitus, dullness to percussion, and a pleural friction rub are sometimes found over the area of the effusion. The posteroanterior and lateral chest radiographs are the most informative initial diagnostic studies when a pleural effusion is suspected. Effusions that blunt the costophrenic angle represent an estimated 200 mL of fluid on posterioanterior radiographs and as little as 50 mL of fluid on lateral imaging. If uncertainty exists, computed tomography and ultrasound may be utilized.

Once the presence of a pleural effusion is confirmed, the etiology should be sought. This is best done through analysis of pleural fluid obtained by thoracentesis. While only a limited number of disorders can be definitively diagnosed by thoracentesis (e.g., malignancy, hemothorax, fungal infection, esophageal rupture, empyema, and tuberculous pleurisy), even nondiagnostic pleural fluid analysis can aid in excluding potential etiologies. Laboratory testing for pleural fluid analysis should include assessment of gross appearance (color and character), cell count, pH, protein level, lactate dehydrogenase level, Gram staining, culture, cytology, and glucose. The fluid should then be categorized as either a transudate or exudate using an algorithm such as the Light's Criteria Rule (see Table 4). The Light's Criteria Rule can misclassify transudative effusions as exudates in some cases of congestive heart failure, and literature review suggests including additional biomarkers to correctly classify pleural effusions in these patients [18]. The use of soluble biomarkers that correlate with specific disease processes may be a useful adjunctive in evaluating the etiology of the pleural effusion [19].

Transudative Effusion

Transudative effusions result from a disparity between oncotic and hydrostatic pressures in the pleural space. Congestive heart failure is the most common cause of a transudative effusion and is usually bilateral. In these patients, the failing left ventricle leads to increased pulmonary capillary pressure that forces fluid into the interstitium; the failing right ventricle contributes to an effusion by elevating capillary hydrostatic force in the parietal pleura, thus diminishing reabsorption. Hepatic cirrhosis is associated with a transudative right-sided effusion in 5–10 % of cases where ascites is present. Pancreatitis

and subphrenic abscesses can also produce right-sided effusions. While these typically begin as transudates, they often convert to exudative effusions. Nephrotic syndrome and hypoalbuminemia produce transudates as part of a generalized process of increased interstitial edema.

Exudative Effusion

Exudative effusions result from inflammation or infiltrative disease processes affecting the pleura, including impaired lymphatic drainage. They are often due to malignancy, most commonly bronchogenic, breast metastases, or mesotheliomas. While most acute bacterial pneumonias do not lead to effusions, a parapneumonic effusion is seen in 5 % of cases of pneumococcal pneumonia. Viral and mycoplasma pneumonia may also cause effusions, as can tuberculosis. Pleural fluid analysis of the patient with pulmonary tuberculosis demonstrates a low glucose and a predominance of lymphocytes. Organisms are rarely found on acid fast stain, and cultures are positive in only 25 % of cases. Pulmonary embolus is accompanied by effusion in 50 % of cases. Typically small and localized to the area of pleuritic chest pain, the embolus may result from localized interstitial edema or bloody exudates due to infarction. Other less frequent causes of exudates include collagen vascular diseases such as systemic lupus and rheumatoid arthritis.

Management

Treatment of a pleural effusion is directed towards management of the underlying disease process. Appropriate antibiotic therapy usually results in resolution of a parapneumonic pleural effusion, although some effusions require chest tube drainage. Pleurodesis is used for management of recurrent malignant effusions and for transudative effusions that do not respond to maximal medical treatment.

Family and Community Issues

Many pleural effusions reflect chronic disease processes, and the family physician is uniquely positioned to aid in care coordination, support, and patient education. Hospice care may be beneficial for the terminal patient. Some infectious diseases including tuberculosis require community level screening and treatment of exposed family members.

Interstitial Lung Disease

The interstitial lung diseases (ILDs) are a group of heterogeneous disorders classified due to similarities in physiologic, clinical, pathologic, and radiographic findings. In the USA, the prevalence of ILD is estimated to be 20–40 per 100,000 persons. Common histologic findings of ILD include derangement of the alveolar structures in the lung with accompanying inflammation (alveolitis) and fibrosis of the alveolar walls, air spaces, and pulmonary capillaries. The initiating agent is unknown in most cases but is thought to be precipitated by a toxin or antigen. These pathophysiologic changes result in decreased lung compliance and volume as well as impaired oxygen exchange.

More than 150 variations of ILD have been identified and are classified by etiology. Sixty-five percent have no known etiology. Table 5 is an abbreviated list of the more commonly seen ILDs.

Diagnosis

A comprehensive evaluation is indicated in all patients with suspected ILD, including thorough patient history, physical examination, laboratory testing when appropriate, and imaging. In most instances, the thorough evaluation will result in a narrowed range of differentials or specific diagnosis which will assist the family physician in clinical decision-making. The patient history must include onset and duration of symptoms, past medical history, current and past medications and radiation exposure, smoking history, occupational and environmental exposures. The clinical symptoms of ILD are progressive dyspnea on exertion and persistent nonproductive cough. Less frequent presenting symptoms include

Table 5 Common etiologies of interstitial lung diseases

Known etiology	Idiopathic etiology
Drug-induced pulmonary toxicity Amiodarone Gold Nitrofurantoin Penicillamine Farmer's lung Hypersensitivity pneumonitis Inhaled inorganic dust Carbon (coal dust, graphite) Metals (aluminum, hard metal dusts, tin) Silicates (asbestos, beryllium, mica, silica, talc) Radiation induced lung injury	Collagen vascular disorders Eosinophilic pneumonitis Histiocytosis X Idiopathic pulmonary fibrosis Rheumatoid arthritis Sarcoidosis Systemic lupus erythematosus

fatigue, chest pain, hemoptysis, fever, anorexia, and weight loss. The pulmonary examination is typically nonspecific and may reveal bibasilar velcro-like rales. Additional examination findings may include clubbing, cyanosis, or extra pulmonary findings consistent with the underlying pathology. The exam may be normal. Laboratory testing should be pursued with a goal to clarify suspected ILD etiology and may include complete blood count with differential, liver function test, basic metabolic panel, creatine kinase, urinalysis, hepatitis serology, HIV screening, ANA, rheumatoid factor, ANCA, anti-JO-1 antibodies, and anti-ds DNA. Arterial blood gases may be normal or demonstrate a mild hypoxemia that worsens with activity. Hypercarbia is rare, and hypocarbia may be present.

Chest radiography may reveal an array of patterns, including nodular, reticular, or mixed findings. The correlation between radiographic pattern and clinical disease staging is limited; however, the evidence of a honeycomb pattern corresponds directly with poor prognosis. A comparison of prior chest imaging is essential to evaluate disease progression. A normal radiograph is present in 10 % of patients with ILD. High resolution computed tomography is considered the gold standard for assessing morphological changes in pulmonary parenchyma and may be helpful in evaluating diffuse ILD. MRI is emerging as an alternative modality to assess the morphological and functional changes of lung parenchyma in ILD [21]. More invasive diagnostic measures can be utilized when clinical indications exist. These include atypical or progressive symptoms, extrapulmonary involvement, and the absence of a plausible clinical diagnosis. Bronchoalveolar lavage has been shown to be an effective diagnostic tool with fewer complications than transbronchial or thoracoscopic lung biopsies [22]. The majority of ILDs demonstrate a restrictive pattern on pulmonary function tests with reduction in vital capacity, carbon monoxide diffusing capacity of the lungs (DL_{C0}), and total lung volume. Forced expiratory volume in first second/forced vital capacity ratio (FEV_1/FVC) may be normal or increased.

Management

The goal of treatment in ILD is to suppress alveolitis and prevent further lung damage. Untreated, most ILDs progress to end-stage lung disease complicated by cor pulmonale and death due to respiratory failure. The mainstay of treatment for ILDs of unknown etiology is corticosteroids to decrease inflammation. Immunosuppressive and cytotoxic agents have also been used. Bronchodilators and oxygen therapy may be useful in late stages of ILD. With known ILDs, initial treatment begins with identification and removal of the causative agent followed by corticosteroid therapy if the inflammation fails to resolve. There is strong evidence that pirfenidone reduces disease progression in patients with idiopathic pulmonary fibrosis [23] and that combined pirfenidone and pulmonary rehabilitation improves the quality of life in patients with ILD [24].

Family and Community Issues

Despite treatment, many patients with ILD will experience poorly controlled pain, dyspnea, and fatigue that can result in social isolation and diminished quality of life. The family physician should aid in identifying supportive and palliative care needs and facilitating end of life discussions to clarify goals of care.

Atelectasis

Atelectasis is a condition involving the loss of lung volume due to the collapse of alveolar space. Atelectasis can be classified by location (lobe or segment location), amount of lung tissue involved (subsegmental or lobar), or pathophysiologic mechanism (obstructive or nonobstructive). Pediatric populations, particularly infants and young children, are at increased risk of atelectasis due to increased chest wall compliance and decreased collateral ventilation of obstructed alveoli as compared to adults. Widespread diffuse atelectasis due to inadequate surfactant occurs in the premature infant with respiratory distress syndrome or from the lung injury of vapor or smoke inhalation.

Segmental and Subsegmental Atelectasis

Diagnosis

Risk factors for segmental and subsegmental atelectasis include abdominal or chest surgery, inadequate preoperative education, chronic lung disease (FEV_1 less than 1.5 L), tobacco exposure, obesity, cardiac disease, age over 55, recent respiratory infection, muscle weakness, excessive secretions, inadequate postoperative pain relief, and sickle cell crisis. In the postoperative setting, other pulmonary complications such as pulmonary embolus, aspiration, pneumonia, and bronchospasm should be considered, particularly if associated with pleuritic chest pain, hemoptysis, hypoxia, hypoventilation, or fever. The clinical symptoms of subsegmental atelectasis include cough, sputum production, fever, and dyspnea. Physical exam findings demonstrate tachypnea and end-inspiratory crackles. Chest radiography exhibits linear densities in the lower lung fields.

Management

Early ambulation and voluntary deep-breathing exercises reduce pulmonary morbidity in the patient with segmental or subsegmental atelectasis. Exercises should include sustained maximum inspiration with incentive spirometry (10 deep breaths with a 3–5 s inspiratory hold every 1–2 waking hours). In the perioperative period, pre- and postoperative deep breathing with cough and postoperative postural drainage have been shown to reduce atelectasis by more than half [25].

Family and Community Issues

Smoking cessation counseling 2 months prior to surgery should be offered to all patients undergoing elective procedures.

Lobar Atelectasis

Diagnosis

Lobar atelectasis in infants most often involves the right upper lobe. Other considerations in the differential diagnosis of lobar collapse in children include foreign body aspiration, congenital malformations of the bronchial skeleton, external compression from vascular or other structures, and chronic inflammation. Recurrent collapse is common in asthma and cystic fibrosis. Atelectasis should be considered when there is worsening oxygenation on mechanical ventilation. On pulmonary examination, lobar atelectasis produces dullness to percussion with decreased vocal fremitus and breath sounds over the affected lobe. Chest radiography may show an elevation of the hemidiaphragm, displacement of fissures and hilum, and shift of the mediastinum toward the collapsed lobe with homogeneous consolidation of the affected lobe.

Management

The treatment of lobar collapse requires attention to diagnosis and management of underlying disease. Chest percussion and postural drainage via physiotherapy can be beneficial. Bronchoscopy aids in foreign body removal and plays a role in direct treatment of obstructive lesions.

Bronchiectasis

Bronchiectasis is a chronic debilitating airway disease with considerable phenotypic diversity. The prevalence of bronchiectasis varies by

country, although appears to have increased in the USA between 2000 and 2007. Prevalence also appears to increase with age, peaking at ages 80–84 years old. The disease is more common in women than men and appears to have the highest prevalence in Asian populations [26]. The mortality rate of bronchiectasis is estimated between 10 % and 16 % and is associated with bronchiectasis or related respiratory failure. Bronchiectasis is characterized by the irreversible widening of one or more bronchi, often preceded by a significant lung injury such as pneumonia (bacterial, tuberculosis, pertussis), airway obstruction (foreign body aspiration), immunodeficiency, or autoimmune disease; however, there are numerous etiologies that can induce or contribute to the development of bronchiectasis (Table 6). Cystic fibrosis, Mycobacterium avium-intracellulare, bronchopulmonary aspergillosis, primary cilia dyskinesia, α_1-antitrypsin deficiency, hypogammaglobulinemia, rheumatoid arthritis, and Sjögren's syndrome are some additional predisposing diseases.

Table 6 Etiologies of bronchiectasis

Airway obstruction
Carcinoid tumor
Foreign body aspiration
Lymphadenopathy
Anatomic abnormalities
Tracheomalacia or Tracheobronchomalacia
Autoimmune disease
Rheumatoid arthritis
Sjögren's syndrome
Systemic lupus erythematosus
Cilia abnormalities
Primary cilia dyskinesia
Connective tissue disease
Tracheobronchomegaly (Mounier-Kuhn syndrome)
Marfan's disease
Cartilage deficiency (Williams-Campbell syndrome)
Hypersensitivity
Allergic bronchopulmonary aspergillosis (ABPA)
Immunodeficiency
HIV infection
Hyperimmunoglobulin E syndrome (Job's syndrome)
Hypogammaglobulinemia
Immunosuppression
Inflammatory bowel disease
Ulcerative colitis
Crohn's disease
Malignancy
Chronic lymphocytic lymphoma
Stem cell transplantation; graft-versus-host disease
Tissue injury
Pneumonia (bacterial, tuberculosis, pertussis)
Childhood infections
Cigarette smoking
Other
Alpha-1 antitrypsin deficiency
Cystic fibrosis
Yellow nail syndrome
Young's syndrome

Diagnosis

Bronchiectasis should be suspected in any patient presenting with chronic productive cough or frequent respiratory infections. Sputum is typically mucopurulent, noncopious, and non-foul smelling, although sputum production is not essential for diagnosis and the nonclassic presentation may include a patient with nonproductive chronic cough. A comprehensive evaluation is indicated in all patients with suspected bronchiectasis, including patient history, physical examination, laboratory testing, and imaging. Additional findings may include wheezing, rhinosinusitis, fatigue, dyspnea, recurrent fever, pleurisy, and hemoptysis. Common physical exam findings include pulmonary rales, rhonchi, or wheezing. The pulmonary examination may vary with cough and posture or be focal and persistent. Laboratory testing should focus on determining the etiology of disease and includes a complete blood count with differential, pneumococcal vaccine titers, immunoglobulin testing (A, E, G, and M), autoimmune evaluation (ANA, RF, aCCP, SSA, and SSB antibodies), alpha-1 antitrypsin level, cystic fibrosis sweat chloride testing (two measurements), CFTR genetic mutation analysis, sputum culture, and smear (bacteria, fungi, and mycobacteria). Bronchoalveolar lavage should be reserved for the patient unable to produce sputum or cases in which imaging appears normal despite high suspicion for the disease. The chest radiograph is abnormal in 91 % of cases and demonstrates patchy infiltrates, dilated and thickened airways (tram lines, ring shadows in cross section), and occasional air-fluid levels. Axial images of HRCT can definitively diagnose

bronchiectasis. PFTs are useful to assess the degree of respiratory impairment due to bronchiectasis and will typically demonstrate an obstructive pattern (reduced or normal FVC, low FEV_1, and low FEV_1/FVC).

Management

The complex clinical manifestations of bronchiectasis, including irreversible lung injury and the inability to clear secretions, necessitate a multifactorial approach to treatment. Management of the disease focuses on: (1) symptom reduction, (2) improvement in quality of life, and (3) prevention of exacerbations. Treatment of the underlying disease process, such as gamma globulin replacement in hypogammaglobulinemia, may aid in delaying or preventing the progression of bronchiectasis. Inhaled bronchodilators, antiinflammatory agents (oral or inhaled glucocorticoids, NSAIDs), antigastroesophageal reflux therapy, and immunizations (influenza and pneumococcal) may be beneficial in some patients. Oral antibiotic regimens are used as preventive therapy in patients experiencing two or more exacerbations within 1 year; a macrolide is the antibiotic of choice (azithromycin 500 mg three times weekly). The role of aerosolized antibiotics in the management of bronchiectasis remains unclear, although early investigations suggest that select inhaled antibiotics may decrease symptoms, lower sputum bacterial density, and improve patient reported quality of life [27]. In acute exacerbations, oral antibiotics are used to reduce both bacterial load and inflammatory mediators, and antibiotic selection should be based on prior sputum culture results (for patients without prior culture data, fluoroquinolones are an appropriate broad spectrum option). While duration of oral antibiotic therapy in the acute exacerbation is ill-defined, first time exacerbations favor a 10-day duration while recurrent exacerbations benefit from 14 days of therapy. Inpatient treatment during an acute exacerbation should be considered for patients demonstrating hypotension, tachycardia, hypoxemia, fever $\geq$38 °C, or failure to clinically improve on outpatient oral antibiotic therapy. While rigorous population-based studies are lacking, airway clearance techniques, particularly high frequency chest wall oscillation (positive expiratory pressure or PEP), are generally recommended and may be beneficial in reducing sputum volume and improving exercise tolerance [28]. Other therapeutic considerations include arterial embolization for life-threatening hemoptysis and lung resection in symptomatic patients who have failed conservative therapy.

Family and Community Issues

Bronchiectasis imposes a notable economic burden on patients and families due to prolonged hospitalizations, frequent outpatient visits, and extensive medical therapy regimens [29].

Pulmonary Sarcoidosis

Sarcoidosis is a multisystem granulomatous disease with no clear etiology or single validated confirmatory test. The condition affects approximately 10–20 per 100,000 persons with women, African-Americans, and individuals aged 20–60 years old most commonly affected. Mortality from sarcoidosis is estimated at 1–5 %. Pulmonary involvement occurs in over 90 % of patients with sarcoidosis and contributes to the bulk of disease-associated morbidity and mortality. Pulmonary sarcoidosis is characterized by noncaseating granulomas which are most frequently found in the alveolar septa, bronchi, and pulmonary vessels and results in the derangement of pulmonary function. While pulmonary sarcoidosis is generally self-limiting and frequently benign, patients with moderate to severe pulmonary involvement suffer from a chronic and debilitating disease that is often difficult to manage.

Diagnosis

A comprehensive evaluation is indicated in all patients with suspected sarcoidosis, including patient history, physical examination, laboratory

testing, and imaging. The most frequent symptoms of pulmonary sarcoidosis are dyspnea, cough, and chest discomfort. Patients may present initially with nonpulmonary symptoms including fever, arthralgias, malaise, and fatigue. Nearly one half of patients with sarcoidosis are identified incidentally on the basis of abnormalities on chest roentgenogram performed for other reasons. Pulmonary exam findings are rare but may include crackles, wheezing, or digital clubbing in advanced disease. Erythema nodosum may be present and is characteristic of acute sarcoidosis.

Laboratory testing should include a complete blood count and differential, liver function testing, blood urea nitrogen, creatinine, glucose, electrolyte panel, serum calcium, and urinalysis. Additionally, serologic testing for HIV and tuberculin skin testing (or interferon gamma release assay) should be performed.

As pulmonary sarcoidosis occurs in 90 % of patients with sarcoidosis, imaging plays an essential role in diagnosis. The most common radiographic finding is bilateral hilar adenopathy. Additional radiographic findings have been organized into a well-known staging system which provides a framework to understand lung involvement [30], although does not correlate to disease progression or prognosis (Table 7). HRCT can aid in further evaluation of chest radiograph abnormalities and identify irregularities in the lung parenchyma. Transbronchial lung biopsy with transbronchial needle aspiration is the preferred diagnostic modality in patients with enlarged mediastinal lymph nodes [31]. Serum angiotensin-converting enzyme levels are elevated in 75 % of patients, although poor sensitivity and insufficient specificity limit its utility as a diagnostic test. PFTs are useful to assess the degree of respiratory impairment and assist in monitoring disease progression. PFTs typically demonstrate a restrictive pattern with reduced DL_{co} and vital capacity.

It is important to distinguish pulmonary sarcoidosis from other granulomatous and infiltrative lung diseases that may have similar clinical presentation. The differential diagnosis must include fungal infections (histoplasmosis, blastomycosis, and *Pneumocystis jirovecii*), mycobacterial infections, hypersensitivity pneumonitis, pneumoconiosis, pulmonary histiocytic disorders, drug-induced hypersensitivity, foreign body granulomatosis, primary immunodeficiencies, and immune reconstitution inflammatory syndrome.

Table 7 Radiographic stages of pulmonary sarcoidosis

	Radiographic findings
Stage I	Bilateral hilar adenopathy[a]
Stage II	Bilateral hilar adenopathy Reticular opacities[b]
Stage III	Reticular opacities[b] Hilar node regression
Stage IV	Reticular opacities[b] Volume loss

[a]Can be accompanied by right paratracheal node enlargement
[b]Typically found in upper lung fields

Diagnosis of pulmonary sarcoidosis consists of three elements: (1) the presence of clinical and radiographic manifestations of pulmonary sarcoidosis, (2) the histopathologic detection of noncaseating granulomas, and (3) the exclusion of other disease processes. Upon diagnosing pulmonary sarcoidosis, clinicians should evaluate the extent of extrapulmonary involvement, including cardiac (electrocardiogram with echocardiography or 24 h Holter monitoring if indicated) and ocular (visual acuity and fundoscopic testing) findings.

Management

The course of sarcoidosis is variable, with some patients experiencing complete resolution in symptoms and others having slowly progressive disease. The approach to the treatment of pulmonary sarcoidosis is a challenge for clinicians due to the complex, multisystem nature of the disease [32]. The majority of patients with pulmonary sarcoidosis do not require therapy due to the absence of symptoms, nonprogression of disease, and likelihood of spontaneous remission. For symptomatic patients with pulmonary sarcoidosis, dyspnea remains the indicator for initiation of therapy. The goal of therapy is to

relieve symptoms and reduce the burden of granulomatous inflammation. Oral glucocorticoids remain the first line therapy for relieving pulmonary symptoms, although steroids have not been shown to modify the overall course of the disease. For this reason, treatment with corticosteroids is usually reserved for patients with worsening symptoms or organ-threatening pulmonary or extrapulmonary disease. The typical initial therapy for symptomatic sarcoidosis is prednisone 0.3–0.6 mg/kg ideal body weight for 4–6 weeks after which the patient should be reassessed (evaluation of symptoms, radiographic imaging, and PFTs). If the reassessment demonstrates stable or improved disease, the dosage can be tapered to 0.2–0.4 mg/kg for an additional 4–6 weeks. A maintenance dose of oral glucocorticoids can be continued at 0.25–0.5 mg/kg per day with reassessment at 4–12 week intervals. Length of therapy in patients who demonstrate positive response to oral glucocorticoids is unknown, although a 12-month treatment course is generally accepted to minimize relapses. There may be a role for inhaled steroids in the treatment of symptomatic pulmonary sarcoidosis; however, there is limited data to support their use. For patients who cannot tolerate glucocorticoids, alternative regimens may include antimalarial drugs (chloroquine, hydroxhycholorquine) or immunosuppressive agents (methotrexate, azathioprine, leflunomide). Complications due to opportunistic infections while on immunosuppression therapy are rare, although clinicians should monitor patients for these risks. Patients with end stage pulmonary sarcoidosis may be candidates for surgical resection, bronchial artery embolization, or lung transplantation. Unfortunately, as many as two thirds of patients will relapse after cessation of treatment.

Family and Community Issues

Studies have demonstrated that treatment of nicotine dependence in patients with active pulmonary sarcoidosis results in restoration of immune responsiveness [33]. This suggests a beneficial role for the family physician in smoking cessation counseling and therapy. In addition, reduction in BMI may contribute to improved PFT results and symptom control in patients with pulmonary sarcoidosis [34].

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Family Medicine
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Gastritis, Esophagitis, and Peptic Ulcer Disease

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Dyspepsia/Epigastric Pain

Gastritis, esophagitis, and peptic ulcer disease (PUD) present commonly with epigastric pain or dyspepsia. Dyspepsia refers to upper abdominal pain or discomfort and may be associated with fullness, belching, bloating, heartburn, food intolerance, nausea, or vomiting. Dyspepsia is a common problem. Despite discoveries about the cause and treatment of peptic ulcer disease, dyspepsia remains a challenging problem to evaluate and treat.

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 non-ulcer dyspepsia (NUD), PUD, gastroesophageal reflux disease (GERD), and gastritis. NUD, PUD, GERD, and gastritis account for more than 90 % 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 45 years or with alarm "red flag" symptoms (i.e., weight loss, dysphagia, persistent vomiting, gastrointestinal bleeding, hematemesis, 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 of PUD (e.g., gastric outlet obstruction or bleeding) or systemic disease (e.g., weight loss, anemia) should be promptly evaluated and, as needed, hospitalized [1–3]. Because age is the strongest predictor of finding "organic" disease on endoscopy, individuals over

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Table 1 Usual daily dosage of antiacid medications

Generic (brand) name	Usual daily dosage (po)
Antacids (Maalox, Mylanta)	15–30 mL, 0.5 and 2 h after meals and at bedtime
Histamine-2 receptor antagonists	
Famotidine (Pepcid)	20 mg bid
Nizatidine (Axid)	150 mg bid
Ranitidine (Zantac)	150 mg bid
Sucralfate (Carafate)	1 g ac and hs
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

the age of 45 years should more readily be evaluated with endoscopy. For the remaining patients there are three commonly used strategies for the evaluation and management of dyspeptic symptoms: (1) empiric therapy including lifestyle modification; (2) evaluation, usually with endoscopy, for a specific cause of the dyspeptic symptoms; and (3) test for *Helicobacter pylori* and treat if positive ("test and treat").

Empiric treatment for dyspepsia consists of standard anti-acid therapy (Table 1). Histamine-2 receptor antagonists (H_2RAs) and proton-pump inhibitors (PPIs) are available over-the-counter and by prescription. If an H_2RA or PPI fails to relieve symptoms, further workup, preferably with endoscopy, should be undertaken.

The second approach to the patient with dyspepsia is thorough evaluation for a specific cause of the dyspeptic symptoms. When available, upper endoscopy is the preferred procedure. Although an upper gastrointestinal (UGI) series is less expensive and may be more readily available, it has a false-negative rate that exceeds 18 % in some studies and a false-positive rate of 13–35 %. In addition, the UGI series is not sufficiently sensitive for detecting GERD and gastritis, two of the most common causes of dyspepsia. A negative UGI does not rule out structural/"organic" disease, and if indicated, further evaluation with upper endoscopy should be pursued. Although more expensive, upper endoscopy has lower false-positive and false-negative rates, biopsies can be undertaken, and testing for *H. pylori* and celiac disease (sprue) can be performed.

The third common approach to the evaluation of patients with dyspepsia is to test for *H. pylori* and treat if positive. (For further information on the evaluation and treatment of *H. pylori*, see below.) This approach is favored [1–3] by recently published reviews.

Gastroesophageal Reflux Disease

Gastroesophageal reflux disease (GERD) is a common problem with a prevalence of reflux of 10–20 % [4]. It is the fourth most common chronic diagnosis seen in primary care [5]. The incidence of GERD increases during pregnancy and with obesity and tobacco use. 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. Exposure to excessive acid or pepsin can lead to damage of the esophageal mucosa, resulting in inflammation and ultimately scarring and stricture formation. Medications (e.g., theophylline, nitrates,

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calcium channel blockers, and β-adrenergic agonists), foods (e.g., caffeine and chocolate), and alcohol may lower LES pressure and lead to GERD – symptomatic or not. Bisphosphonates may cause local irritation of the esophagus. GERD may occur as an isolated entity or as part of a systemic disorder such as scleroderma. GERD is a risk factor for 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.

Diagnosis

A young patient with no evidence of systemic illness typically requires no further workup and can be treated empirically. Older patients, particularly those with the complaint of odynophagia or dysphagia, require evaluation to rule out tumor or stricture. Upper endoscopy is the evaluation of choice. 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.

Management

GERD is treated by both non-pharmacologic and pharmacologic means [4, 6]. 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. Patients who experience nocturnal symptoms often find relief by putting the head of the bed on blocks 4–6 in. 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. Routine avoidance of foods that can lower LES pressure is no longer recommended.

Patients who do not respond to lifestyle changes alone are treated with pharmacologic agents. 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. For persistent or severe symptoms, PPIs are the mainstay of treatment. H_2RAs can be tried first and, if ineffective, PPIs can be substituted. Once a patient's symptoms are controlled, a trial of decreasing the dose of medication (e.g., from twice daily to once daily) or switching from the more expensive PPIs to less expensive H_2RAs may be warranted. There are concerns regarding long-term PPI use such as declining bone mineralization.

H_2RAs 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. In more severe GERD, PPIs are more efficacious than H_2RAs for symptom control

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including extra-esophageal manifestations and esophageal healing and reducing the risk of stricture formation and recurrence. 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. PPIs are the treatment of choice for erosive esophagitis. Side effects (chiefly headache and diarrhea) resulting in medication discontinuation are rare. As is true for H_2RAs, all available PPIs at equivalent doses are roughly comparable in terms of clinical efficacy. Patients unresponsive to one H_2RA or PPI may be responsive to another agent within the same medication class. Rarely, patients unresponsive to PPIs respond to H_2RAs.

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.

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 or baclofen 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 nonadherent to medical therapy are suitable operative candidates. Laparoscopic fundoplication surgery has been shown to be effective, at least in the short term [7]. Bariatric surgery for obesity may also be helpful [4].

Peptic Ulcer Disease

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. In the past, PUD was marked by periods of healing and recurrence. Successful treatment of ulcers associated with *H. pylori* infection greatly diminishes recurrences.

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

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with ulcer healing as documented by endoscopy. 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. Auscultation of the abdomen may reveal a succussion splash which is due to a mixture of air and fluid in the stomach which may be due to gastric outlet obstruction – a rare but potentially serious complication of peptic ulcer disease when the ulcer arises in the pyloric channel or duodenum. 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.

Diagnosis

There are two ways that PUD may be diagnosed. First, an ulcer may 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 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 (CLOtest) 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. The second approach to PUD is test and treat. A patient is tested for *H. pylori* and if positive, antibiotic therapy can be initiated without documenting an ulcer. There are three methods for testing for *H. pylori* infection: urea breath test, serology, and stool antigen testing. The stool antigen test is more accurate than serology tests. Urea breath test, using a carbon isotope (^{13}C or ^{14}C), is the most accurate noninvasive test (sensitivity 97 %, specificity 100 %) [8, 9]. The use of proton-pump inhibitors, bismuth preparations, and antibiotics can suppress *H. pylori* and lead to false-negative results.

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. A falling ELISA titer (1, 3, and 6 months after therapy) may also be used to document eradication. If a repeat endoscopy is performed, a CLOtest may be used.

Treatment

All patients with PUD who smoke should be advised to stop smoking as continued smoking can delay the rate of ulcer healing. 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 either an H_2RA or 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 (Table 2) [8–10]. A PPI is part of every antibiotic regimen. Patients with *H. pylori*-negative ulcers are treated with traditional antiacid agents without antibiotics for 4–6 weeks. Treatment of *H. pylori* in patients with NUD (with negative endoscopy) is controversial.

Table 2 Treatment for eradication of *Helicobacter pylori-a*ssociated peptic ulcer disease

Therapies with proton-pump inhibitor (PPI)
PPI + metronidazole 500 mg bid + clarithromycin 500 mg bid
PPI + amoxicillin 1 g bid and clarithromycin 500 mg bid
PPI + bismuth subsalicylate 525 mg bid + metronidazole 500 mg bid + clarithromycin 500 mg bid
PPI bismuth subsalicylate 525 mg bid + metronidazole 500 mg bid + tetracycline hydrochloride 500 mg qd

Note: All regimens are given for 10–14 days. All regimens are full dose of PPI twice daily

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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. There is a trade-off between better adherence with the shorter duration of therapy and better eradication rates with a longer duration of 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 triple-drug regimens.

For patients with PUD and no documented *H. pylori*, all H_2RAs 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. Healing rates with sucralfate (Carafate) are comparable to those with H_2RAs. There are no significant side effects although recommended dosing regimens of up to four times daily are likely to limit adherence.

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.

Refractory Ulcers and Maintenance Therapy

Most duodenal ulcers heal within 4–8 weeks of the start of pharmacologic therapy. After 12 weeks of pharmacologic therapy, 90–95 % of ulcers are healed. Higher doses of H_2RAs (e.g., ranitidine 600–1,200 mg/day) or PPIs may be used in an effort to heal refractory ulcers. Gastric ulcers heal more slowly than duodenal ulcers, but 90 % are healed after 12 weeks of pharmacologic therapy. PPIs are the drug of choice for gastric ulcers.

Individuals with persistent or recurrent symptoms after pharmacologic therapy should be reevaluated. Adherence with previous treatment recommendations and avoidance of NSAID use should be reviewed. 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 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

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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 "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 through the GI tract, causing digestion of blood. Melena may also be caused by 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 or any other cause of cirrhosis/portal hypertension such as nonalcoholic steatohepatitis (NASH, "fatty liver" – increasingly common and frequently associated with obesity and the metabolic syndrome) and portal vein thrombosis. 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.

A nasogastric tube can be placed and the aspirate tested for blood. Absence of blood may mean that the bleeding has ceased. The routine placing of a nasogastric tube for diagnosis or lavage has been questioned [11].

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

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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, push endoscopy or 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, interventional, radiological (such as embolization), or surgical (resection or shunting) interventions should be considered.

There are two additional therapies for bleeding varices [12]. 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.

Gastric Cancer

While the incidence of distal gastric cancer has declined significantly in the United States since the 1930s, there has been an increase of proximal stomach cancers. Individuals moving from Japan to the United States lower their risk of gastric cancer, suggesting that dietary and environmental factors play roles in the pathogenesis of this disorder. Additional risk factors include *Helicobacter 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.

Surgical treatment is the only definite chance for a cure. Adjuvant chemotherapy with or without radiation for patients undergoing tumor resection may be recommended.

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Diseases of the Small and Large Bowel

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1 Infectious Diarrhea Syndromes

After upper respiratory tract infections, acute gastroenteritis is the most common illness in the United States. Most cases are brief and self-limited. However, the attack rate is estimated at 1.5–1.9 attacks per person per year and is ultimately responsible for 10,000 deaths per year nationally [1]. Viral organisms are the most common cause of infectious diarrhea; however, the bacterial pathogens *Shigella*, non-typhoidal *Salmonella*, *Escherichia coli*, *Campylobacter jejuni*, and *Yersinia* account for the most severe episodes. Protozoal gastroenteritis caused by *Entamoeba histolytica* and *Giardia lamblia* is common in travelers and may cause intermittent symptoms.

1.1 Clinical Approach to the Patient with Acute Diarrhea

The history and physical examination should be directed to address the following questions:

1. Does the diarrhea originate in the small or large intestine? Small bowel pathology is most often associated with frequent large-volume stools described as watery and often following oral intake of any kind. Large bowel diarrhea is associated with even more frequent stools but of smaller volumes (1–2 l/day) and may be associated with tenesmus and even bloody stools.
2. Are there other contacts with similar illness? Viral diarrhea and food-borne causes of diarrhea commonly present in clusters of affected patients. This is especially true for infections contracted in daycare centers, schools, or healthcare institutions.
3. Has there been recent travel? Possible causes may include enterotoxigenic *E. coli*, protozoans *E. histolytica* or *G. lamblia*, or other parasitic infestation.
4. Has there been any consumption of undercooked hamburger meat or poultry? This might suggest *Salmonella* or enterohemorrhagic *E. coli.*
5. Has there been any antibiotic use within the preceding 8 weeks, suggesting a post-antibiotic colitis with *Clostridium difficile* overgrowth?
6. Are there any other predisposing medical conditions for diarrhea, especially diabetes, HIV disease, or bowel surgery?

If the illness proves to be prolonged rather than self-limited, consider the following diagnostic investigations:

1. A stool sample for culture, as well as ova and parasites. This is a simple first step, overlooked by many office clinicians, and, although inconvenient for the patient, provides a foundation of diagnostic information.

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2. A stool sample for *C. difficile* toxin, especially in the elderly patient or someone with a recent antibiotic history.
3. In cases that are culture negative, consider anoscopy/rigid sigmoidoscopy with direct visualization of the rectal mucosa. These are simple examinations, taking just minutes to perform, in the clinic or the Emergency Room, and provide information about the condition of the bowel mucosa. More seriously ill patients may require flexible sigmoidoscopy or even colonoscopy to visualize the bowel and obtain biopsies.
4. If no colon pathology is identified, consider upper GI endoscopy with small bowel biopsies or a small bowel barium enema and follow-through radiologic exam looking for small bowel mucosal pathology.

2 Parasitic Infections of Small Bowel

Parasitic infections of the small bowel are most commonly caused by hookworm (*Ancylostoma* or *Necator* spp.), tapeworms (Cestoda), pinworm (*Enterobius* spp.), and strongyloidiasis (*Strongyloides* spp.). Worldwide, these parasites infect over a billion persons and may cause significant morbidity, especially in children and pregnant women. They are invariably associated with depressed living conditions which include contaminated water supplies, undercooked meats, institutionalization, and poor sanitation facilities.

Hookworm infestation is the most common cause of iron-deficiency anemia in the developing world. Walking barefoot over areas used for human defecation allows the worm to enter the body by penetrating the feet. The worm settles into the small intestine, and symptoms include abdominal pain and diarrhea. Blood work reveals a hypochromic, microcytic anemia. Diagnosis is made by observation of worms or their eggs in a stool sample. Treatment is with mebendazole, albendazole, or pyrantel pamoate. Ivermectin is not active against hookworm.

Tapeworms generally use cattle, pigs, or fish as their hosts. Humans eating undercooked meats containing tapeworm eggs or ingesting water contaminated with tapeworm eggs or larvae may get infected. Inquire about recent travel to underdeveloped areas and working with livestock. Generally, patients will present with nonspecific symptoms such as diffuse abdominal pain, weight loss, and diarrhea; in some cases, pork tapeworm cases may present as a myositis or even a seizure disorder depending on where the parasite has concentrated. Diagnosis is made by examination of stool for ova and parasites. Treatment is with praziquantel, albendazole, or nitazoxanide.

Pinworms (*Enterobius vermicularis*) are the most common worm infestation in developed countries and usually affect young children in daycare or school settings. The most common symptom is anal itching, which is typically worse at night, as the adult worms come out of the anus to copulate on the perineal skin. The worm is transmitted by ingestion of eggs, usually picked up from sharing objects with an infected individual who has performed less than adequate handwashing after wiping or touching their anal area. The eggs may also become airborne from clothing or bedding and be inhaled into the aerodigestive tract. Diagnosis is made by identification of worms or their eggs on a slide made from the perineal area. Treatment is with albendazole or mebendazole and should be offered to the entire family to prevent reinfection.

Strongyloidiasis, or roundworm infection, is caused by the helminths *Strongyloides* sp. The worms are found worldwide, and the most common pathway of infection is contact with soil that is contaminated by *Strongyloides* larvae. Typical risk factors include walking barefoot over contaminated soil, having contact with untreated human waste or sewage, and working with contaminated soils in farming or mining occupations. Common symptoms include abdominal pain, bloating, diarrhea, and nausea or vomiting;

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sometimes, a recurrent red raised skin rash is present along thighs and buttocks. Diagnosis is made from microscopic inspection of stool for larvae; serology is available for diagnosis, and an elevated eosinophil count is often present. Treatment choices consist of ivermectin, thiabendazole, albendazole, and mebendazole. The parasite should be treated even in the absence of symptoms, as hyperinfection carries a high mortality rate [2].

3 Protozoal Infections

The most common causes of protozoal gastrointestinal infection in the United States are *Entamoeba histolytica* and *Giardia lamblia. Entamoeba* infection may produce either an intermittent diarrheal syndrome or a more severe, fulminating illness with a presentation similar to inflammatory bowel disease. Giardiasis produces a more chronic diarrheal illness often accompanied by epigastric symptoms of pain and cramping due to duodenal infestation with the parasite. There is often a travel history which provides valuable historical clues in detecting these illnesses. Amebiasis is common in travelers to the tropics, while giardiasis is endemic to freshwater sources in some Western nations, most notably Russia. Giardiasis may also present in daycare settings, campers who have had contact with freshwater streams, and the severely immunocompromised (i.e., advanced HIV patients). Amebiasis may produce occult or frank blood in the stool, and proctoscopic exam may reveal a friable and erythematous rectal mucosa. Definitive diagnosis is made from an examination of fresh stool, with identification of cysts or trophozoites. Amebiasis is treated with metronidazole, 750 mg po tid for 10 days, followed by iodoquinol, 650 mg po tid for 3 weeks. Giardiasis may be treated with metronidazole 250 mg po tid for 5 days or quinacrine 100 mg po tid for 5 days.

4 Viral Infections

4.1 General Principles

Viral enteric infections are responsible for the majority of gastrointestinal complaints seen in the office or emergency department. Patient complaints include diarrhea, nausea, vomiting, fever, abdominal cramping and/or pain, headache, and malaise. Viral gastroenteritis ranges from a self-limited watery diarrheal illness usually lasting less than a week to a more fulminant illness with intractable vomiting and dehydration resulting in hospitalization or even death. There are three general settings of viral gastroenteritis. The first is a sporadic gastroenteritis in infants, which is most commonly caused by rotavirus. The second is an epidemic gastroenteritis that occurs either in semi-closed populations (families, healthcare institutions, cruise ships) or as a result of food- or waterborne pathogens including noroviruses and caliciviruses. The third is a sporadic acute gastroenteritis of adults, which is usually due to infection with caliciviruses, rotaviruses, adenoviruses, or astroviruses.

4.2 Diagnosis

Physical examination of the patient may reveal hyperactive bowel sounds and mild lower abdominal discomfort with palpation. If history and physical examination are insufficient to make a diagnosis, obtain a complete blood count (CBC) and a stool sample. The CBC often reveals a normal white blood cell count with a slight lymphocytosis, although elevations of the white cell count into the upper teens are possible. Microscopic examination of the stool sample should reveal an excess of water without pus or blood.

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4.3 Treatment

Treatment should focus around rehydration, either orally or parenterally. In many cases, the nausea and vomiting associated with the gastroenteritis are a barrier to oral rehydration. The use of ondansetron (Zofran®) in a dose of 4–8 mg every 4–6 h as the orally dissolving wafer is very useful in settling the nausea and allowing oral rehydration. The medication is effective within 20–30 min. Appropriate oral rehydration solutions follow the WHO guidelines of sodium/potassium/glucose ratios. The WHO solutions are commercially available (Gastrolyte®, Pedialyte®) or can be made at home from distilled water, 6 teaspoons of sugar, ½ teaspoon of salt, and ½ cup (125 ml) of orange juice in 1 l of clean water. Parental 0.9 % saline or Ringers lactate solutions are also appropriate for more advanced cases. In most cases, the diarrhea may subside in 3–5 days. The role of antidiarrheal agents is controversial and does nothing to hasten resolution of the illness [3].

5 Bacterial Infections

Bacterial enteric infections are associated with symptoms of diarrhea, vomiting, and abdominal discomfort. The symptoms result as a direct effect of bacterial toxin on the intestinal wall stimulating secretion of water into the intestinal lumen or by actual invasion of the bacteria into the intestinal wall.

5.1 *Escherichia coli*

This bacterium causes diarrhea by either of the previously mentioned mechanisms. At least five forms of gastroenteritis may result, including enteropathogenic, enterotoxigenic, enteroinvasive, enterohemorrhagic, and enteroadherent types. Diagnosis is often difficult, because *E. coli* is found commonly in stool as normal flora. The enterotoxigenic type of gastroenteritis is associated with travel (traveler's diarrhea), while the enterohemorrhagic variety is often associated with undercooked poultry or hamburger meat. Most cases of coliform gastroenteritis are brief, and the associated fever, diarrhea, and abdominal cramps are self-limited; however, the very young patient and the elderly patient may have a much more fulminant illness with frankly bloody diarrhea, dehydration, and possible acute hepatorenal failure. These patients will need prompt hospital admission and aggressive fluid management.

In patients with significant symptoms and suspected invasive disease, a Gram or Wright stain of the stool reveals numerous polymorphonuclear leukocytes and erythrocytes. Stool culture is necessary, and treatment is supported with oral/parenteral fluid replacement and analgesia. Chronic cases of *E. coli* enteritis may require antibiotic therapy for resolution (ciprofloxacin 250–500 mg po bid for 7–10 days is a reasonable choice) [4].

5.2 *Salmonella*

Five distinct clinical syndromes are associated with *Salmonella* infections: (1) gastroenteritis (about 75 % of infections); (2) bacteremia with and without gastrointestinal involvement (10 % of cases); (3) typhoidal "enteric" fever (85 of cases); (4) localized infections in bones, joints, and meninges (5 %); and (5) a symptomatic carrier gallbladder state.

Salmonella enterica, serovar Typhi, produces a typical gastroenteritis with headache, nausea, vomiting, diarrhea, and fever lasting for 2–4 days. Solid food restriction, analgesia, and fluid and electrolyte repletion are effective treatment. Other serotypes may produce a more severe illness lasting up to 3 weeks, occasionally accompanied by bacteremia. Stool examination in these cases will reveal fecal leukocytes, and culture is required to identify the organism. Antibiotics are not required in those with only mild illness and no evidence of bacteremia. Patients with more severe illness or documented bacteremia may require hospitalization for parenteral fluid replacement and antibiotics. Reasonable choices include

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ciprofloxacin, 400 mg IV q12h for 10 days, or ceftriaxone 1–2 g IV daily AND azithromycin 500 mg IV/po daily for 3–5 days.

5.3 *Campylobacter jejuni*

Campylobacter jejuni is probably the most common cause of inflammatory diarrhea in developed countries. Infection may vary from an asymptomatic case to severe enterocolitis. A typical episode begins with fever and malaise, followed within 24 h by nausea, vomiting, diarrhea, and lower-quadrant abdominal pain. The diarrhea may be profuse, contains plenty of leukocytes, and is often frankly bloody tinged. Infection is usually self-limited and lasts 5–7 days. Reservoirs of infection include contaminated water, milk, meat, and poultry; also implicated are domestic pets, particularly cats and dogs. Diagnosis is not always obvious from history, physical examination, or typical initial lab work, which may reveal a significant leukocytosis. Stool culture is required for diagnosis. Treatment includes fluid replacement and analgesia. Indications for antibiotic treatment include high fever, prolonged course of symptoms >7 days, increasingly bloody stools, or history of immunocompromise, including HIV. Antibiotic treatment choices include azithromycin, 10 mg/kg/day (adults simplified to 500 mg daily 3 days), or ciprofloxacin, 500 mg po bid 7 days. Clindamycin is also an alternative, 150–300 mg po tid 7 days [5].

5.4 *Yersinia*

Yersinia enterocolitica is responsible for a spectrum of illnesses, ranging from simple gastroenteritis to invasive ileitis and colitis. In older children and adults, *Yersinia* infections may cause a mesenteric adenitis, with symptoms mimicking acute appendicitis. Diarrhea is a fairly constant feature, often with accompanying fever and abdominal crampy pains. Duration of illness lasts 14–46 days. *Yersinia* may cause radiographic findings mimicking Crohn's colitis, including bowel wall nodularity, mucosal thickening, and aphthous ulceration. The illness is usually self-limited, and antibiotics are generally not necessary. In patients who have significant clinical illness or severe radiographic changes, antibiotic choices include TMP-SMX 1–2 tablets bid, third generation oral or parenteral cephalosporins, or ciprofloxacin.

5.5 *Shigella*

Shigella organisms may cause a severe, invasive diarrhea (dysentery), especially in infants and the elderly. The diarrhea is frequent, bloody, and mucoid, due to invasion of the colonic epithelium by the organism. The clinical course is biphasic, beginning with watery diarrhea, malaise, and fever; this is followed by tenesmus and frank dysentery within 24 h. Children tend to have a milder infection, lasting 1–3 days; adults may suffer symptoms for 7 days. In severe cases, symptoms may persist for 2–4 weeks. The stool will contain pus and blood, and a stool culture is mandatory for accurate diagnosis. Therapy includes fluid and electrolyte repletion, as well as antibiotics. Antibiotic choices that include third generation oral or parenteral cephalosporins, ciprofloxacin, TMP-SMX, or ampicillin are reasonable, effective, and readily available. Treatment should be continued for 14 days [6].

6 Conditions Associated with *Clostridium difficile* Infection

6.1 General Principles

Clostridium difficile is associated with a colitis that usually follows broad-spectrum antibiotic usage for unrelated conditions. The colitis is associated with a persistent diarrhea, causing significant morbidity and a not-insignificant mortality rate among affected patients, the majority of whom are elderly persons. When the normal bacterial flora of the colon is altered by antibiotics, *Clostridium difficile* overgrows and

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releases a toxin which causes mucosal inflammation and damage. Diarrhea follows this damage and may last for weeks, with significant dehydration, abdominal pain, and weakness. *Clostridium difficile* infection (CDI) occurs primarily in hospitalized patients, but may be seen in the community. By CDC estimates, a 30 % reduction in the use of broad-spectrum antibiotics would result in a 26 % decrease in CDI [7].

6.2 Diagnosis

Diagnosis of CDI should be suspected in any patient with persisting diarrhea who has received antibiotics within the previous 3 months, has been recently hospitalized, or has a recurrence of diarrhea 48 h or more after hospital discharge. Physical examination of these patients reveals varying degrees of dehydration and abdominal tenderness. Patients may appear frankly septic. Rigid proctosigmoidoscopy or flexible endoscopy reveals an inflamed and edematous colonic wall with raised yellow-white pseudomembranes (hence the previous term for this condition as pseudomembranous colitis). Laboratory findings generally reveal a leukocytosis, electrolyte disturbances, and often a raised serum lactate, especially in those with colonic megacolon or ischemia from CDI. Stool assays are confirmative, with most hospital and outpatient labs offering a rapid enzyme-linked immunoassay for the detection of glutamate dehydrogenase (which is produced by *C. difficile*) or stool toxins produced by the bacteria. The best radiologic examination is CT scanning of the abdomen with IV contrast enhancement. CT generally reveals a markedly thickened and inflamed bowel wall with visualization of colonic wall lesions and sometimes areas of ischemic change. Plain radiographs are useful in demonstrating areas of colonic distention (diameter $>$10 cm) or megacolon, which has a more grave prognosis.

6.3 Treatment

Treatment of CDI begins with fluid and electrolyte replacement and ensuring there is no area of bowel ischemia that would require urgent surgical consultation. Stabilized patients with only mild diarrhea and no fever, abdominal pain, or leukocytosis can be managed supportively, with immediate discontinuation of any preceding antibiotic therapy. Patients with mild to moderate diarrhea associated with radiographic changes of colitis and leukocytosis/pain will require cessation of preceding antibiotics, as well as oral metronidazole (500 mg po tid 10–14 days) or oral vancomycin (125 mg po qid for 10 days). In patients with aggressive disease and significant complications of megacolon/ischemia/sepsis, inpatient admission with both IV metronidazole (500 g tid) and po or rectal vancomycin (500 mg po or pr qid) may be required.

Relapse occurs in 20–30 % of patients, despite appropriate initial therapy. First relapse should be treated with metronidazole +/− oral vancomycin, depending on the severity of the relapse. Subsequent relapses should be treated with pulse-dose vancomycin, or fidaxomicin 200 mg po bid for 10–14 days.

Since the last edition of this chapter, a new therapy for recurrent CDI has proven to be superior to antibiotic therapy. The therapy is fecal microbiota transplantation (FMT), and the concept is not a new one. FMT has been used sporadically by practitioners throughout the ages, but only recently has been systematically studied and applied to CDI patients. Briefly, FMT requires a distillate of stool from a healthy donor being transplanted into the small or large bowel of the recipient. The fecal material from the donor recolonizes the bowel of the patient with normal flora and is nearly always associated with a dramatic resolution of symptoms and the return of normal bowel health [8]. FMT may be delivered via NG tube, in an appropriately packaged oral form (“crapsules”), or by enema. Donors should be thoroughly screened for multiple conditions, including Hepatitis A, B, and C, as well as HIV. Although the FDA currently at the time of this writing considers FMT to be an investigational treatment, multiple Internet websites are available which actually walk the general public through giving themselves a fecal transplant from an unscreened community donor. It is probable that commercially prepared, medical-

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grade fecal material will be available for patient use within the next few years, and FMT will be standard of care for CDI.

7 Malabsorption

Malabsorption syndrome refers to the inability to absorb or digest one or more nutrients. Inability to absorb certain nutrients leads to a high osmotic load within the bowel and results in the presenting symptoms. The segment of involved intestine specifies the extent of the malabsorption.

Diarrhea is the most common symptom of malabsorption. It is usually watery and of moderate volume. Steatorrhea is the result of fat malabsorption and is characterized by pale, malodorous stools which float on the surface of the toilet water. Weight loss and fatigue are a physiologic follow-up to malabsorption, and patients may try to compensate by increasing caloric content. Flatulence and abdominal distention result from the fermentation of undigested nutrients into methane and other gases. Edema may result from chronic protein malnutrition or obstruction of small bowel lymphatics. Anemia is common and may be microcytic or macrocytic, depending on the segment of the involved bowel. Malabsorption syndromes have recently been linked to neurologic manifestations resulting from electrolyte disturbances, vitamin malabsorption, or antigen-antibody complexes resulting from the body's own immunologic response to contact with certain nutrients (Table 1).

8 Celiac Sprue and Controversies Regarding Gluten

8.1 General Principles

Celiac sprue is also known as celiac disease and gluten enteropathy. It is estimated to affect 1 % of the population and is a chronic disease of the digestive tract. There is a hereditary component, with 10 % of first-degree relatives having the disease. The pathophysiologic changes of this disease are seen in the small bowel, with destruction of intestinal villi and lengthening of the intestinal crypts. The degradation of absorptive surface of the small bowel leads to symptoms of maldigestion and malabsorption. The cause of these pathophysiologic changes is an immunologically mediated inflammatory response to gliadin, an alcohol-soluble fraction of gluten. Gluten is a protein found in wheat, rye, and barley and is among the most heavily consumed proteins on Earth, providing roughly 20 % of all the calories consumed by people. Thus, for individuals who manifest this inflammatory condition, consumption of any gluten-containing product causes further trouble.

Celiac sprue has a variable spectrum of presentation, with some individuals having minimally troubling or even undetectable symptoms, while other people are quite disabled, with the inflammatory sequelae affecting multiple organ systems. The most common symptoms include chronic diarrhea, cramping,

Table 1 Correlating malabsorption syndromes to symptoms

Diarrhea	Most common symptom
Steatorrhea	Whipple's disease, pancreatic failure
Weight loss	Whipple's disease, pancreatic failure, sprue, celiac disease, inflammatory bowel disease
Flatulence and distention	Lactose intolerance, celiac disease
Edema	Pancreatic failure
Microcytic anemia	Celiac disease
Macrocytic anemia	Crohn's ileocolitis
Neurologic symptoms, rashes	Celiac disease

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weight loss, fatigue, skin rashes, growth abnormalities, anemia, bleeding diatheses, neurologic symptoms (seizures, paresthesias, motor weakness), and osteopenia. There is a bimodal age distribution of the disease, the first at 8–12 months and then between 20 and 40 years of age. Some patients appear to have minimal symptoms and findings under middle age, when diagnosis becomes more obvious.

8.2 Diagnosis

Diagnosis relies in no small measure in keeping celiac sprue as part of a differential diagnosis of abdominal pain and diarrhea. A good history is essential, as physical exam may provide few clues. Workup should be performed while the patient is still consuming gluten. This maximizes the return on workup, as presumably the patient has ongoing inflammatory changes. A CBC and metabolic profile should be performed, with attention to levels of serum proteins, calcium, magnesium, iron, and cholesterol. Antibody testing, with the presence of IgA anti-tissue transglutaminase (IgA TTG), is the best first test, and if positive, small bowel biopsies obtained through upper GI endoscopy are required for confirmation. In patients younger than 2 years of age, combine IgA TTG with testing for IgG-deamidated gliadin peptides (DGP IgG). Measurement of endomysial IgA and reticulin IgA should also be performed to quantitate mucosal damage. Stool studies looking for fecal fat are helpful to document steatorrhea, and orally administered absorption studies like D-xylose or lactose are useful in quantifying carbohydrate malabsorption. On the cutting edge is genetic testing with confirmatory serology. The presence of HLA-DQ2.5 with positive IgA TTG and DGP IgG has strong specificity and sensitivity for the disease. The best single radiologic study for diagnosis is a barium small bowel follow-through, which usually shows dilatation of the small intestine and a coarsening or even obliteration of the fine mucosal pattern [9].

8.3 Treatment

Treatment is based on a gluten-free (no products containing wheat, rye, or barley in any form) diet. In refractory patients, corticosteroid administration may help; if there is still no response despite steroids, consider other possibilities such as small bowel lymphoma.

There has been a recent trend in both the mainstream North American press and various medical writers over the last several years to implicate gluten as a relative culinary “poison.” These writers contend that gluten is responsible for multiple medical conditions, including arthritis, asthma, schizophrenia, multiple sclerosis, and inflammatory bowel disease. Many patients may present to the clinic complaining of vague digestive symptoms that have abated after they stopped consuming gluten, thus coining the condition labeled “non-celiac gluten sensitivity.” This condition is difficult to quantify histologically or biochemically and seems to follow a pattern of self-diagnosis. Management of patients who believe they have gluten sensitivity is conservative. It is unlikely they will comply with a diet containing gluten to maximize laboratory testing to actually prove the existence of a true medical condition, so allowing them to follow a diet of their choice with periodic bland reassurance from the medical perspective seems the least contentious [10].

9 Irritable Bowel Syndrome

9.1 General Principles

Irritable bowel syndrome (IBS) is a common gastrointestinal problem encountered by family physicians. Patients with IBS may have some, or all, of symptoms including: abdominal pain, distention, altered bowel habit, urgency, flatus, and a sense of incomplete evacuation. Synonymous terms include spastic colon, mucous colitis, and irritable colon. Patients with IBS have disordered motility of the entire gut. IBS

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Table 2 Rome III criteria for diagnosis of IBS

Relieved by defecation
Onset associated with a change in stool frequency
Onset associated with a change in stool form or appearance
Altered stool frequency
Altered stool form
Altered stool passage (straining and/or urgency)
Mucorrhea
Abdominal bloating or subjective distention

has no underlying anatomic abnormality or inflammatory component; however, patients with IBS tend to have some element of secondary psychiatric morbidity, with anxiety, depression, and somatization being the most common. IBS is typically found in young or middle-aged adults, with a 2:1 female-to-male ratio.

9.2 Clinical Presentation

The hallmark of IBS is abdominal pain associated with defecation. Diagnosis is delineated by the Rome III criteria and requires at a minimum that patients have abdominal pain or discomfort at least 3 days per month during the previous 3 months that is associated with the symptoms listed in Table 2. The pain is reliably relieved by defecation, and there is invariably a change in the frequency of stool and a change in stool form. The frequency of stool is usually more than three bowel movements daily or less than three movements per week. IBS has four distinctive bowel patterns: IBS-D (diarrhea predominant), IBS-C (constipation predominant), IBS-M (mixed diarrhea and constipation), and IBS-A (alternating diarrhea and constipation), and it is not uncommon for patients to switch between subtypes over the course of a year.

9.3 Clinical Approach to the Patient with Suspected IBS

The extent of investigation depends on how closely the history and patient physical examination fit the defining characteristics of IBS. Typically, the physical examination is normal, apart from some vague lower-quadrant tenderness and perhaps some palpable bowel loops. Features on history and physical examination that argue against IBS include a steady downhill course, significant weight loss, nocturnal symptoms, onset after age 60, cachexia, or abdominal mass. Basic laboratory workup includes obtaining a CBC, comprehensive metabolic profile to look for electrolyte abnormalities, serum albumin (to rule out a malabsorptive condition), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), stool culture, stool for *C. difficile* toxin, and stool for ova and parasites. Colonoscopy is indicated for those patients over age 40, especially if symptoms are of recent onset or if there is a history of bowel malignancy.

9.4 Management

IBS is a chronic illness, with periodic exacerbations. Successful management requires a strong relationship between patient and provider. Management must be individualized and directed toward reduction of symptoms as well as reduction of secondary anxiety, which is invariably present. After an appropriate workup, reassurance that there is no serious pathologic process at work is very helpful. Dietary restrictions are probably unnecessary, except in cases of lactose intolerance. However, useful dietary interventions include fiber supplementation to improve symptoms of diarrhea and constipation, judicious water intake, caffeine avoidance, and avoidance of legumes to reduce flatulence. Psychological interventions, cognitive behavioral therapy, dynamic psychotherapy, and hypnotherapy are all more effective than placebo and may be of value. Pharmacologic interventions which have some value in the management of symptoms

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include anticholinergics (dicyclomine and hyoscyamine), tricyclic antidepressants (amitriptyline, imipramine), prokinetic agents (metoclopramide, domperidone), antidiarrheals (loperamide, diphenoxylate), serotonin 5-HT3 receptor antagonists (alosetron), chloride channel activators (lubiprostone), guanylate cyclase C agonists (linaclotide), and antispasmodics (peppermint oil, pinaverium, trimebutine, cimetropium/dicyclomine). Generally, no one agent is a panacea, and most patients will require ongoing reworking/refinements of various medications over the years for adequate symptom control [11, 12].

10 Diverticular Disease

10.1 General Principles

Diverticulosis of the colon results from herniation of the mucosal and submucosal layers through the muscularis layer. This often occurs at points where nutrient arteries penetrate the muscularis. The incidence of diverticulosis in Western populations increases with age and is observed to include roughly 65 % of individuals by age 85. Diverticulitis is the inflammatory complication of diverticula and is seen in 20 % of persons with diverticulosis. The risk of diverticulitis increases with the number and distribution of diverticula. The exact cause of diverticulosis is elusive, but risk factors include obesity, a low-fiber diet, and constipation.

10.2 Clinical Presentation

Colonic diverticula are generally asymptomatic and found incidentally on colonoscopy or other imaging study of the colon. The most common location is over the length of the sigmoid colon in Western populations, where colonic intraluminal pressures are the highest; however, in Asian populations, diverticula are more common along the right side of the colon. Inflammation of a diverticulum results from an impaction of the diverticular sac from some colonic debris. The impaction results in increased susceptibility of the thin-walled diverticular sac to invasion by colonic bacteria. This in turn leads to microperforation of the sac wall with localized inflammation (peridiverticulitis), localized peridiverticular abscess formation, or, in some cases, wider inflammation with pericolonic abscess formation. Most of the time, only one diverticulum is involved, and the inflammation remains localized, healing with a residual area of pericolic fibrosis. Repeated attacks of diverticulitis may lead to segmental narrowing of the colon and possible obstruction.

Diverticulitis with a large perforation may lead to pericolonic abscess, which can extend along the bowel wall or rupture into adjacent organs, creating fistulas between the colon and vagina, urethra, bladder, or overlying abdominal wall. Rarely, free perforation of a diverticulum may occur and present with frank peritonitis.

Patients with acute diverticulitis present with pain, usually in the left lower quadrant. Right lower-quadrant pain may also occur; consider right colon disease or even appendicitis. Signs of peritoneal irritation, fever, leukocytosis, and possibly a palpable mass may also be present in advanced cases.

10.3 Diagnosis

A patient history, physical examination, and an awareness of the disease provide a starting point for diagnosis. For an acute episode, consider a CBC, basic metabolic profile (to define any dehydration or renal issues), and a computed tomography (CT) scan of the abdomen and pelvis with IV contrast. CT scanning is very helpful in making the diagnosis and delineating the extent of disease. Common CT scan findings may include pericolic fat stranding due to inflammation, diverticula, bowel wall thickening, soft tissue inflammatory masses or phlegmons, abscesses, and fistulas. See Fig. 1 for an example of a CT

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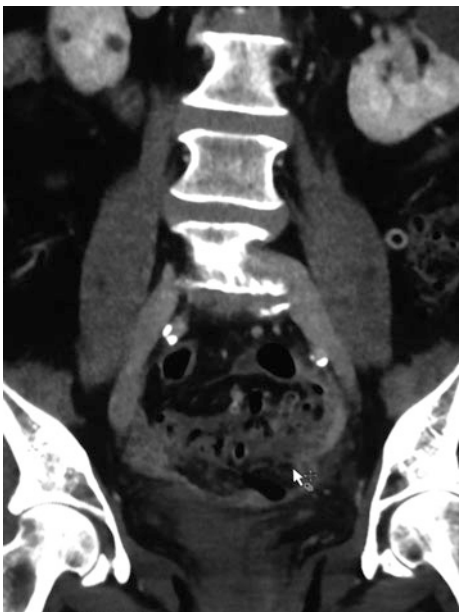

Fig. 1 This is an IV-contrasted scan, sagittal plane. Note the multiple sigmoid diverticula; the arrow points at a small area of abscess formation (Image courtesy of David James MD)

image of diverticulitis with a small pericolic abscess. Plain abdominal radiographs are less helpful, but are useful to delineate any free air under the diaphragm or bowel obstruction.

In nonacute cases, flexible sigmoidoscopy, colonoscopy, or air contrast barium enema will reveal the disease, as well as helping to rule out other disorders such as inflammatory bowel disease or colonic carcinoma. Keep in mind that a common cause of colonic bleeding is from a ruptured diverticulum. The right colon is the source of 70 % of these bleeds, which are usually duller red and copious. Luckily, these are a low-pressure venous bleed and are usually self-limiting. Obviously, urgent colonoscopy should be scheduled as soon as the bleeding stops to investigate the bleeding source.

10.4 Treatment

Asymptomatic patients do not require any specific treatment apart from general advice to increase dietary fiber intake. Patients with only mild tenderness, no leukocytosis, and no fever may be managed as outpatients, with oral antibiotics. Acutely ill patients will need inpatient management and a surgical consultation. See Table 3 for treatment options [13, 14].

11 Microscopic Colitis

11.1 General Principles

Microscopic colitis is the term used to describe patients who have persistent unexplained non-bloody diarrhea. These patients will have an endoscopically and radiologically normal-appearing colon, but biopsies show unique inflammatory changes. Microscopic colitis was previously known as collagenous colitis (CC) and lymphocytic colitis (LC). The characteristic feature of LC is the infiltration of lymphocytes into the colonic epithelium; CC shares this finding, but in addition, there is a thickening of the subepithelial collagen table. Whether LC and CC represent a continuous spectrum of the same disease process remains an unproven theory. Incidence is relatively rare and is most commonly found in people over the age of 40. LC affects men and women equally, while CC is 20 times more frequent in women than

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Table 3 Management options in diverticulitis

Mild diverticulitis, localized tenderness, no peritoneal signs	No fever, leukocytosis, CT scan showing little or no inflammatory changes	Outpatient management acceptable	TMP-SMX 1 DS tablet po bid PLUS metronidazole, 500 mg po bid, OR Ciprofloxacin 500 mg po bid PLUS metronidazole 500 mg po bid, OR moxifloxacin 400 mg po daily, OR amoxicillin/sulbactam 875 mg po bid, ALL for 10 days
Moderate disease, regional tenderness, localized peritoneal signs	Fever, leukocytosis, CT scan suggesting localized inflammation, no abscess or perforation	Inpatient management advisable	Ciprofloxacin 400 mg PLUS metronidazole 500 mg IV q12 h, OR Ceftriaxone 1 g 1–2 g daily PLUS metronidazole 500 mg IV q12 h, OR Piperacillin/tazobactam 4.5 g IV q6–8 h, OR Ertapenem, 1 g daily, OR meropenem 1 g IV q8 h
Severe disease with pan-abdominal tenderness and peritoneal signs	Fever, +/−leukocytosis, elevated serum lactate, CT scan suggesting abscess formation, perforation with free air	Inpatient management and surgical consultation mandatory	IV antibiotics as above

men. Consequences of this condition are limited to the stress of ongoing diarrhea and malabsorption and may include weight loss, electrolyte abnormalities, dehydration, and chronic fatigue. Most of these patients will have had diarrhea for years, with multiple consultations and radiologic studies before diagnosis is made from endoscopically obtained colonic tissue biopsies of the rectosigmoid and ascending colon, and most have been labeled as diarrhea-prominent IBS.

11.2 Etiology

No specific etiology has been determined, but some evidence suggests that certain antidepressant drugs (SSRIs and sertraline) may increase the risk of CC. Other drugs, notably ranitidine, proton pump inhibitors, ticlopidine, ASA, flutamide, simvastatin, carbamazepine, and lisinopril, have also been implicated. Other patients may have other autoimmune conditions including uveitis, autoimmune thyroid disease, idiopathic pulmonary fibrosis, juvenile DM, and pernicious anemia. One-third of patients with celiac disease also have histologic findings consistent with microscopic colitis, and the diagnosis of microscopic colitis should be considered in those patients with a presumptive diagnosis of celiac disease in whom diarrhea does not resolve after elimination of gluten from the diet. A gluten-free diet does not seem to treat microscopic colitis in the absence of celiac disease.

11.3 Treatment

Treatment is graduated, and it should be noted that some patients have clinical courses marked by spontaneous remissions and relapses. Drugs known to be associated with microscopic colitis should be stopped before other treatment is started. See Table 4 for management options [15].

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Table 4 Management steps in microscopic colitis

Step 1: Symptom control	Loperamide or diphenoxylate/atropine as needed
Step 2: Moderate disease and persisting symptoms	Bismuth subsalicylate 2–3 262 mg tabs qid 2 months, mesalamine 3 g/day 8 weeks, and/or cholestyramine 8 g/day
Step 3: More severe colitis	Budesonide 9 mg daily 6 weeks with no taper, OR prednisone 60–80 mg/day for 2 weeks, with a tapering dose for a further 2 weeks
Step 4: Refractory disease and symptoms	Azathioprine 2 g/kg/day or methotrexate 15 mg/M^2 BSA po/IM twice weekly

12 Inflammatory Bowel Disease

12.1 General Principles

Inflammatory bowel disease includes at least two forms of idiopathic intestinal inflammation: ulcerative colitis (UC) and Crohn's disease (CD, also known as regional ileitis). Etiology appears to be a dysregulated immune response to host intestinal microflora. There is an increased incidence in persons with asthma or COPD, and persons with IBD are at higher risk for the development of bowel malignancy. Prevalence varies between 5 and 10 per 100,000 persons. Both disorders occur equally in men and women, with spikes of peak incidence between the ages 15 and 30 and then again between ages 55 and 65.

The manifestations of IBD generally depend upon the segment(s) of intestinal tract involved. Symptoms are not specific, but may include:

- Irregular bowel habit, predominantly with bouts of diarrhea often with passage of mucus
- Intestinal cramping and abdominal pains
- Fever and sweats
- Malaise, fatigue, and progressive weight loss
- Arthralgias, and in the case of CD, extra-intestinal manifestations such as arthritis, osteoporosis, uveitis, dermatitis, or liver disease
- Growth retardation and delayed or failed sexual maturation in children
- Grossly bloody stools
- Perianal disease, abscess, and fistula formation (50 % of those with CD)

12.2 Clinical Presentation

12.2.1 Crohn's Disease

Crohn's disease (CD) produces a transmural inflammation of the alimentary tract anywhere along its length, with ulceration of the mucosa and formation of granulomas, fistulas, and abscesses. The inflammation may be segmental, with relatively normal tissues interposed between involved areas ("skip lesions"). Involvement of the terminal ileum and colon is common. Pain is more frequent in the right lower quadrant and may be associated with a palpable mass due to chronic inflammation.

12.2.2 Ulcerative Colitis

In contrast to CD, UC produces a nontransmural inflammation of the mucosa and superficial submucosa, typically of the rectum and distal colon. Inflammation may occur proximally, extending into the right colon. Major symptoms include abdominal pain, fever, rectal bleeding, diarrhea, and tenesmus. The severity of symptoms correlates with the intensity of inflammation and extent of bowel involved.

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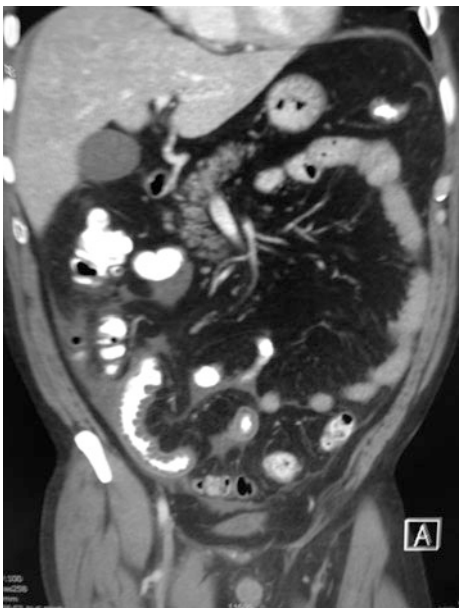

Fig. 2 Sagittal CT scan with IV and oral contrast demonstrating a thickened terminal ileum typical of Crohn's ileocolitis with substantial inflammatory changes to supporting mesentery; note also the free fluid around the liver and in the pelvis (Courtesy of David James MD)

12.3 Diagnostic Approach

Diagnosis of IBD requires a careful history, a general physical examination of the patient, and appropriate laboratory, radiologic, and endoscopic examinations. Stool examination is important, as other conditions may mimic IBD. Stool samples are generally heme positive, with microscopic examination revealing neutrophils and eosinophils. Colitis caused by bacterial pathogens as *Salmonella*, *Campylobacter*, *C. difficile*, or protozoans (amebiasis) may mimic IBD, so a stool examination for ova and parasites and a stool culture are prudent. Laboratory investigation begins with a CBC and metabolic panel. Expect a mild anemia with a microcytic smear from chronic low-volume blood loss and an elevated WBC from the chronic inflammatory (rather than infectious) condition. Serum proteins may be decreased, especially in CD, from chronic malabsorption from small bowel inflammation. Similarly, serum B_{12} levels may be depressed from poor vitamin uptake in a diseased ileal region of the bowel. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels will be elevated, and they can be used serially to assess the general level of inflammation. In children, there is some evidence for using the level of fecal calprotectin levels to diagnose IBD.

Radiologic evaluation is important in making the diagnosis. Plain films form a foundation in the workup. In UC, plain films may reveal irregularity of the colonic wall, with telltale "thumbprinting" due to local bowel wall edema. Occasionally, air in the bowel wall (pneumatosis coli) or even free air from perforation may be seen. Megacolon is defined by a bowel luminal diameter of 10 cm or greater and is a serious complication of UC which may require surgical intervention. In CD, plain films may reveal nephrolithiasis, osteopenia, or sacroiliitis. Air contrast films will reveal the extent of colonic disease in CD and define the presence of fistulas, submucosal edema, and pseudodiverticula formation. Upper GI studies with oral contrast and follow-through technique are useful for the definition of small bowel disease in CD. CT scanning with a minimum of IV contrast is an ideal study to define the presence and extent of bowel pathology in UC and CD and is often the initial radiologic evaluation of an ill patient in the emergency department setting (see Fig. 2). CT scanning is also the ideal modality to reveal associated IBD pathology, including abscesses, fistulas, mesenteric edema/streaking, free fluid, and bowel wall

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thickening. CT enterography is a CT contrast study wherein the patient ingests a substantial amount of oral contrast prior to scanning. This technique allows careful examination of the small bowel and is replacing plain film follow-through upper GI enemas as a diagnostic modality to define small bowel pathology. Magnetic resonance imaging (MRI) has been shown to be equivalent to endoscopy in predicting severity and extent of colonic disease, edema, and fistulas. MRI has a higher sensitivity than CT or endoscopy to delineate the pelvic and perirectal complications of CD. MR enterography is also a choice when radiation exposure from repeated CT scanning may be an issue [16].

12.4 Management

The management of inflammatory bowel disease has become increasingly sophisticated over the last decade and is best approached as a team, involving frequent collaborative consultations with gastroenterology and surgical specialists. Most patients will require a combination of both medical and surgical therapies over the course of their lifelong disease. The medical approach for IBD includes symptom relief and therapy to produce mucosal healing. Usually, a stepwise escalation of medical therapy is required until a response is achieved. The two primary goals of therapy are remission (induction) and prevention of disease flares (remission). Surgical therapy is indicated for patients who fail medical therapy and suffer from disease complications.

Current trends in management emphasize deep mucosal healing, especially in CD. Combination therapy using both anti-TNF (tumor necrosis factor-like) agents and immune modifiers earlier in the course of IBD may result in elimination of inflammation, reduction in surgical procedures, and reduction in hospitalization for many patients.

Patients with IBD will require symptomatic therapy, especially when active inflammation is not related to symptoms. Treatment with antidiarrheal agents (loperamide or diphenoxylate) should be avoided, as they may produce toxic megacolon in individuals with significant colonic inflammation. Antispasmodic medication (hyoscyamine, dicyclomine, scopolamine) may be used for symptomatic relief. In patients with significant ileal disease from CD, diarrhea may be due to bile salt malabsorption, and cholestyramine resin may be helpful.

12.5 Stepwise Approach to IBD Therapy

The first step in IBD therapy is an aminosalicylate. No one aminosalicylate has been shown to be superior, so mesalamine, 500–1,000 mg po qid for 8 weeks, is a reasonable first choice. It is more effective in UC than CD and will not maintain a remission of CD. Mesalamine is also available in enema and suppository form and is useful for the treatment of localized distal colitis. For CD, the addition of metronidazole 500 mg bid-tid PLUS ciprofloxacin 500 mg po bid for 2–4 weeks has been shown to be helpful, especially if the patient has perianal disease or an inflammatory mass on abdominal CT scan (refer again to Fig. 2 for an illustration).

If the patient fails to respond to aminosalicylates in an appropriate dose, addition of corticosteroids as a second step follows. Depending on the extent of the disease flare, 10–60 mg po of prednisone daily is indicated. Once a clinical response is seen, the dose should be tapered and then ceased. If the patient relapses during the steroid taper, the next step of therapy, immune-modifying agents, needs to be considered.

Immunomodulating agents include azathioprine, 6-mercaptopurine, cyclosporine A, tacrolimus, and methotrexate. Consideration should be given to the use of anti-TNF agents (infliximab, adalimumab, golimumab, or certolizumab pegol) or the integrin antagonist, vedolizumab, if disease flares are frequent (two or more flares per year), if the patient requires a prolonged or more intense steroid dosage, or if the patient's bowel inflammation appears to be refractory to steroids. Immune modifiers generally have a 2–3

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month onset of action and are not appropriate for induction of a remission. These agents are of value in primary treatment of fistulas in CD and maintenance of remission.

The use of immunomodulating agents requires a thorough patient evaluation prior to initiation of use. In particular, patients require screening for occult tuberculosis, hepatitis, or intra-abdominal abscesses. Frequent monitoring of hematologic values (CBC) and liver function is required. Patients requiring step 3 therapy benefit from concurrent care from a gastroenterologist with knowledge of advanced IBD therapy [17].

Surgical therapy is curative for UC. However, as CD can involve any part of the alimentary tract from mouth to anus, surgery is only a stopgap and may lead to complications such as recurrent bowel obstruction from adhesions or short gut syndrome. In UC, surgery is indicated for intractable colon inflammation unresponsive to medical therapy, intolerance to medical therapy, perforation, toxic megacolon, or precancerous changes on colonoscopy. The most common surgical choices are proctocolectomy with ileostomy and total proctocolectomy with ileoanal anastomosis. In this last option, a multistage procedure involves performing a diverting ileostomy and creating an ileal pouch that is anastomosed directly to the anus. The rectum and its mucosa are removed. After the ileoanal anastomosis is healed, the ileostomy is taken down, and flow through the anus is reestablished. In female patients planning to get pregnant, proctocolectomy with ileostomy is preferred, as it avoids the extensive pelvic dissection and high subsequent infertility rate with ileoanal anastomosis.

In CD, surgery is indicated for disease complications (fistula, stricture), rather than for a primary cure. Approximately 70 % or more of patients with CD will require surgery, and modern techniques emphasize bowel-length sparing procedures. In patients with severe perianal disease, a diverting ileostomy or colostomy is an option that improves their quality of life. Percutaneous abscess drainage and endoscopic balloon dilatation of strictures are options in carefully selected patients. Involve surgical consultants early with these patients, and remember that medically refractory disease is a relative contraindication for surgery [18].

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Family Medicine
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Diseases of the Pancreas

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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].

Approach to the Patient

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 of these 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].

History and Physical

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].

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Laboratory Studies and Testing

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 h 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 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 h), the presence of shock, gastrointestinal bleeding, pulmonary insufficiency, or renal failure; and (3) severe, persistent organ failure (greater than 48 h). 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 h to correct third spacing and maintain an adequate intravascular volume. Fluid requirements should be reassessed at frequent intervals – within 6 h of admission and for the next 24–48 h – 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

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pancreatitis, necrotic pancreas, or organ failure, enteral nutrition should be started within 48 h: [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, metronidazole) is strongly recommended as soon as possible after a severe attack [5].

Causative Therapy

Early endoscopic retrograde cholangiopancreatography (ERCP), preferably within 24 h, 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].

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]. The incidence of chronic

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pancreatitis is between 5 and 12 cases per 100,000 persons per year, which accounts for more than 120,000 outpatient visits and 50,000 hospitalizations annually [10].

Causes

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

History/Physical Exam

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

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 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].

Imaging

Diagnosis can be confirmed by pancreatic calcifications on imaging (abdominal plain film or CT) or a pancreatogram revealing beading or ectatic 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

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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, autoimmune 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 opiates 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.

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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 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 Presentations

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. Malignant 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 of Pancreatic Cysts

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].

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IPMN

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.

MCN

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 5 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, a provider can consider screening individuals from families with known genetic defects predisposing them to pancreatic cancer or with familial pancreatic cancer. Expert opinion recommends screening with CT or EUS [38].

Clinical Manifestations

Abdominal pain, jaundice, pruritis, dark urine, and acholic stools may all be presenting symptoms as a result 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

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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].

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 have resectable disease, 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 palliation (i.e., adequate nutrition and pain control), which may have some effect on survival.

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Family Medicine
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Diseases of the Liver

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Diseases of the liver encompass a wide variety of clinical conditions that range from mild abnormalities on liver testing to end-stage liver disease 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.

"Liver function tests" 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/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 a second test. 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 factors, 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.

1 Viral, Alcoholic, and Drug-Induced Liver Disease

1.1 Hepatitis A

Hepatitis A virus (HAV) is an RNA enterovirus that is a common worldwide disease affecting the liver, spread through fecal-oral contamination with occasional outbreaks through food sources. It can range in severity from a mild illness lasting a few weeks 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].

1.1.1 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

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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 Caucasion 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

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].

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 5,000 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.

1.1.2 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.

1.1.3 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

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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), users of injection drugs, people with chronic liver disease such as hepatitis B or hepatitis C, 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, 6].

Postexposure prophylaxis is available if a health individual has been exposed to HAV within the past 2 weeks as prophylaxis efficacy beyond this time is not well known. The preferred prophylaxis by the Center for Disease Control (CDC) is a single dose of single-antigen vaccine for individuals between 12 months and 40 years of age, but immunoglobulin may also be used [5]. 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, and food handlers in facility with confirmed case; however, schools, hospitals, and work settings are not appropriate for prophylaxis with an episode of a single case [5, 7].

1.2 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. 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, individuals with IV drug use, those living with someone with chronic HBV, infants born to infected mothers, individuals exposed to blood through their work, patients on hemodialysis, and those traveling to countries with moderate to high rates of HBV infection.

1.2.1 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 [8]. 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 [8].

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 [9]. The risk of development of CHB infection is lowest in adults (<5 %) and highest in neonates whose mothers are HBeAg positive (>90 %) [10]. 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

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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

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
Anti-HBc	Positive	Interpretations[a]
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

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. Physical examination should be directed at evaluating for stigmata of chronic liver disease (CLD) such as jaundice, splenomegaly, ascites, peripheral edema, encephalopathy, or signs of portal hypertension.

Current thinking endorses that there are phases of CHB infection including an immune tolerant phase, immune reactant phase, inactive HBV carrier state, HBeAg-negative CHB, and HBsAg-negative phase [8, 11]. 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

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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.

1.2.2 Management

The role of the family physician largely in the management of HBV, both acute and chronic, is correct 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, and evidence is not present for overall effects that such screening improves overall survival. A liver biopsy is often necessary to determine the extent and severity of disease 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. Current treatments include conventional interferon alpha, pegylated interferon alpha, and nucleoside/nucleotide analogues (NUCs), most notably lamivudine. 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) [9] and the European Association for the Study of the Liver (EASL) [11].

1.2.3 Prevention

Vaccination remains a significant mechanism of prevention of HBV infection. Its enormous impact was demonstrated with reduction of the incidence in acute HBV infection in the USA from 300,000 cases annually to 79,000 cases annually from the late 1980s to 2001 [13]. Vaccination is recommended for all children and adolescents, adults in certain ethnic groups, health care workers, and high-risk groups [14].

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 cesarian 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.

1.3 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 IVDA; HIV; recipients of blood transfusion, blood products, or organs before

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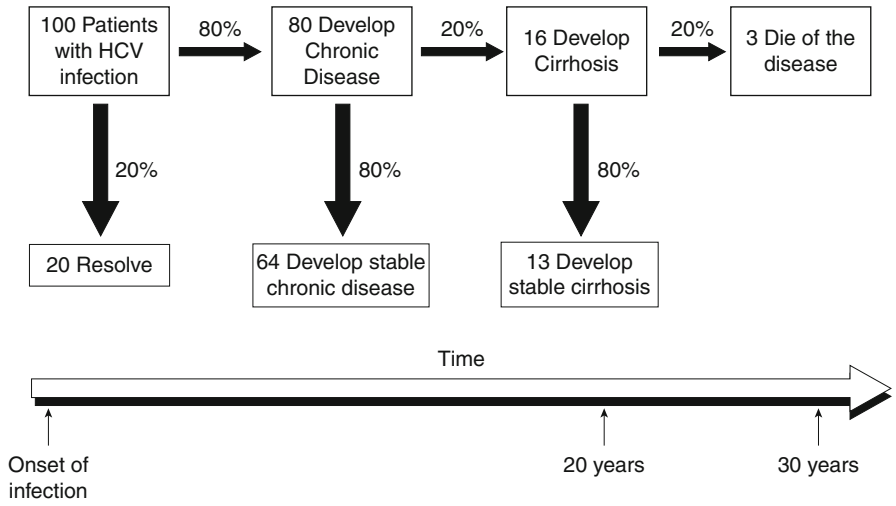

Fig. 1 The natural history of HCV infection is said to follow the "80/20 rule." While this is representative of population data, the percentages are approximate and vary based on several cofactors

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 HBV.

1.3.1 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 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.

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1.3.2 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. 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 [20]. A number of methods are available to determine the degree of fibrosis with liver biopsy previously serving as the diagnostic standard; however, there remain significant concerns about performing a liver biopsy on an individual with normal transaminases, and inadequate sampling can limit test performance [21]. The most appropriate approach is to combine vibration-controlled transient liver elastography with direct serum biomarkers [22]. Biopsy is reserved when these two measures are discordant in their assessment of cirrhosis or inflammatory damage.

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 USA 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) [23]. It is important to note, however, that significant recent advancements have occurred in the development of regimens for the treatment of HCV infection that are now being utilized as first-line therapies. 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 in 2014 led to even newer therapies, potentially removing the need for ribavirin use as well, including sofosbuvir (Sovaldi) and simepravir (Olysio), sofosbuvir/ledipasvir (Harvoni), and partiaprevir/ombitasvir/dasabuvir (Viekira Pak). 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 [23].

1.3.3 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 be offered to all adults born between 1945 and 1965 due to high prevalence in this population [24].

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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, [25], 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 [26].

1.4 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 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.

1.5 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 [27]. 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, [28], lesser amounts can potentially result in ALD as regular consumption of 30 g/day increases the risk for development of cirrhosis [27].

1.5.1 Clinical Presentation and Diagnosis

Given that excessive, regular alcohol consumption is necessary, most patients with ALD are often between 40 and 50 years old [29]. 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

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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 & Oral contraceptives
	Testosterone
Rheumatolic agents	Methotrexate
	Quinadine
Psychiatric agents	Atypical antipsychotics (quetiapine, etc)
	Nefazodone
	Trazodone
	Venlafaxine

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.

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1.5.2 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.

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 and pentoxifylline have been shown to demonstrate improvements on mortality in specific populations with disease [31]. Despite evidence suggesting these treatments have efficacy, their use remains controversial. 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.

1.5.3 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. 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"[32].

1.6 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 [33]. 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 1,000 drugs have caused liver disease on more than one occasion, [34] and therefore a comprehensive list is not easily developed. Table 4 lists some of the more common drugs that can induce liver damage.

1.7 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 [35]. 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 [35]. This is largely secondary to fibrosis and complication rates in patients coinfected with HIV and either HBV or HCV being much higher [36]. 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).

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Table 5 Risks of HAART on liver disease

NRTIs		NNRTIs	
Caution	Didanosine (ddl)	*Caution*	Nevirapine (NVP)
	Stavudine (d4T)		Efavirenz (EFV)
	Zidovudine (ZDV/AZT)	*Safer*	Etravirine (ETV)
	Zalcitabine (ddC)		Rilphirine (RPV)
Safer	Abacavir (ABC)		
	Tenofovir (TDF)	**Protease inhibitors (Pi's)**	
	Lamivudine (3TC)	*Caution*	Ritonavir (RTV;/r)
	Emtricitabine (FTC)		Telapravir (TPV)
		Safer	Indinavir (IDV)
Integrate inhibitors			Atazanavir (ATAZ)
Safer	Raltegravir (RAL)		Saquinavir (SQV)
	Elvitagravir (EVG)		Lopinavir (LPV)
	Dolutegravir (DTG)		Darunavir (DRV)
			Amprenavir (APV)
Entry inhibitors			Nelfinavir (NFV)
	Maraviroc (MVC)		
	Enfuvirtide (INN;T20)	**Enhancer**	
			Cobicistat (COBI)

In addition to infectious etiologies, increasing recognition of highly active antiretroviral therapy (HAART) as a source of liver damage 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 [37]. Additionally, many patients with HIV whose liver enzymes are elevated are asymptomatic during this time [38]. 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 [39].

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, [40] and is noted to have significantly higher rates in those infected with HIV compared to the general population [41].

1.8 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; [42] however, HCC secondary to HCV infection is a significant cause of cancer-related death in the USA, 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, other diseases affecting the liver are also potential risk factors. 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 [44].

1.8.1 Clinical Presentation and Diagnosis

Almost all patients with HCC have underlying cirrhosis, and therefore 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

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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 [45]. As previously noted, it is increasingly recognized that alpha-fetoprotein lacks adequate sensitivity and specificity to be utilized as a screening or diagnostic aid [46]. 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 [47].

1.8.2 Management

Based on the staging at diagnosis (Barcelona Clinic Liver Cancer (BCLC) staging system), [48] there are several potentially curative or palliative approaches to treatment [49] 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.

1.8.3 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.

2 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. Indeed, 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 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 his 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.

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3 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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Family Medicine
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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 found 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 nerve feedback from the hemorrhoidal cushions helps differentiate between flatus, liquid, and solid stool [3]. Aging and repeated 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 continued trauma by feces and ulcerates, sometimes causing bright red rectal bleeding.

Epidemiology

Hemorrhoids are most common in both sexes between 45 and 65 years of age with hemorrhoid-related symptoms being experienced by nearly one in two Americans over 50 [4]. 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 hemorrhoids.

Classification

Hemorrhoids may be located above (internal) or below the dentate line (external) or both above and below (intero-external) [5]. Based on symptoms of bleeding and prolapse, hemorrhoids are classified as grade 1 or first degree (bleeding without mucosal prolapse), grade 2 or second degree (bleeding and mucosal

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prolapse reducing spontaneously), grade 3 or third degree (bleeding and mucosal prolapse, requiring manual reduction), and grade 4 or fourth degree, representing persistent prolapsed hemorrhoids with or without complications (strangulation, ulceration, fibrosis, gangrene, sepsis) [5, 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. Features of anemia should suggest 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, perianal excoriation, fistula, cancer, or condyloma. Patient bearing down during DRE or anoscopy relaxes the sphincter and also causes second- and third-degree hemorrhoids to prolapse. Uncomplicated hemorrhoids are impalpable and non-tender; 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 [8].

Treatment: Nonoperative

Adequate fluid and fiber intake (20–35 G daily) is the primary first-line nonoperative therapy for patients with symptomatic hemorrhoids of all grades [5]. Multiple symptoms associated with 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 after hemorrhoidectomy [9]. 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 its complications [10, 11]. Exercising and losing excess weight are also beneficial.

Office Procedures

The rubber-band ligation (RBL) technique is useful in treating grades 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,

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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 (85 %) patients, though over one-third may require repeat banding [12]. 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 replication), 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 or 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 grades I, II, and III hemorrhoids, the majority of patients over time experience recurrence [13]. Complications include mucosal sloughing, thrombosis, abscess formation, and bacteremia.

Infrared photocoagulation (direct application of infrared waves) produces superficial tissue destruction, reducing blood flow and tethering the hemorrhoid to the underlying tissues. It is most useful in grades I and II hemorrhoids [5].

In-Hospital Surgery

Hemorrhoidectomy is indicated in patients with intero-external hemorrhoids and grades III and IV hemorrhoids, in patients recurring after office procedures, or in patients intolerant of office procedures [5]. The procedure, performed under general or regional anesthesia, requires distal bowel preparation to minimize soiling during and after surgery. 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]. 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, and recurrence rates are similar to conventional hemorrhoidectomy [15]. The Doppler-guided transanal hemorrhoidal ligation involves suture ligation of the hemorrhoidal vessels after localizing them with Doppler ultrasound. This procedure, also applicable to grades III and IV hemorrhoids, allows most patients to be discharged at 24 h and return to work in 2–3 days. Long-term recurrence is under 10 %, though higher for 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

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hemorrhoidectomy. Immediate excision leads to excess tissue removal, anal canal narrowing, and infection. Spreading perianal infection and tissue necrosis occasionally occur, 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 >8–12 weeks) [17]. Anal fissures are more common in younger adults and have an equal sex distribution. The majority (over 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 [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 nonhealing fissures.

Diagnosis

Diagnosis is clinical. Severe pain initiated by and persisting 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

Nonoperative treatment improves pain and bleeding, heals fissures in nearly 50 % of patients, and is advocated initially in both acute and chronic fissures [17]. Measures include fiber 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 ointment, when combined with Botox injection, induces lasting healing in most chronic fissures [19]. Surgery is, however, consistently superior to medical therapy in chronic fissures and may be offered without initial conservative treatment failure [17].

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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 nonoperative 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 less 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

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 [20]. 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 [21]. 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) [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) [22]. Anorectal abscesses may be perianal, ischiorectal, intersphincteric, or supralevator. A perianal 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.

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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 and systemic symptoms [23]. Physical examination in perianal abscess 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.

Treatment

Incision and drainage as an office procedure (under local anesthesia with or without conscious sedation) is the treatment of choice in perianal abscess [22]. The incision is deepened to enter the abscess cavity; any slough is removed, the cavity 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 [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) left in the fistulous tract, and the abscess cavity is allowed to heal.

The diagnosis of supralevator (pelvic) abscess usually requires initial confirmation by imaging (US or CT) to delineate its extent and determine the underlying cause (colitis, 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. Nearly 80 % 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, 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 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].

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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. The "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. 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.

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].

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 for at least 1 month, in an individual with a developmental age of at least 4 years [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

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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 indicate 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, inflammatory bowel disease, and neoplasms. Colonoscopy is recommended in patients over 50 years.

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 (aging, disease, or trauma) Proctitis (inflammatory bowel disease, radiation) Psychiatric disorders	Pelvic floor dysfunction, altered stool characteristics, anorectal hypersensitivity, willful soiling, functional incontinence

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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.

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. 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 (70–80 % of patients improve) [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 full continence in nearly half (47.2 %) 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 nonhealing 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

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(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 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

Nonoperative 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 transanal 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 fit 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

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

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promontory, inducing fibrosis and minimizing risk of recurrent prolapse and fecal incontinence. Rectopexy also helps heal rectal ulcers. Coexisting uterovaginal prolapse may also be corrected (rectocolpopexy).

Perineal procedures (mucosal sleeve resection, Delorme procedure, and perineal proctosigmoidectomy, Altemeier procedure) are useful in patients 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 (two- to fourfold increase) 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 conditions (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 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 with 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.

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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].

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 detect 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 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. Antioxidants (vitamins A, C, and E) reduce diarrhea and tenesmus and supplement the beneficial effects of other treatment measures [45]. Hyperbaric oxygen improves symptoms by enhancing tissue oxygenation, impeding bacterial overgrowth and toxin production, and stimulating angiogenesis. When administered (90 min at 2 atm daily five times a week), considerable improvement is noticed; these patients require less medication or other invasive treatment measures [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 involve a diverting colostomy, strictureplasty, or pelvic exenteration [45].

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Table 4 Treatment options in proctitis Ref. [44–47]

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

Hidradenitis Suppurativa

Background

Hidradenitis suppurativa is a chronic recurrent inflammatory skin disorder affecting the hair and areas carrying apocrine sweat glands and adjacent connective tissue; perineal involvement occurs more often in men [48]. 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 infection or Crohn's disease may coexist.

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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 child-bearing 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 [48].

Condyloma Acuminatum

Background
Anal condyloma acuminatum (warts) is caused by sexual (usual) or nonsexual transmission of the human papillomavirus (HPV), typically low-risk subtypes 6, 11, 42, 43, and 44 [49]. Most (90 %) are caused by types 6 and 11. 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
Patients with 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. 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 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

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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.

Multiple patient-applied local therapies (podofilox 0.5 % solution or gel applied twice daily for 3 days a week – 4 such cycles, imiquimod 5 % cream applied daily at bedtime for 16 weeks, sinecatechin 15 % ointment applied three times daily for 16 weeks) are available. 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 health-care 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 [49–51].

Anal Canal Cancers

Squamous cell carcinoma (SCC) is the most common type of malignancy in the anal canal followed by the cloacogenic, basaloid, epidermoid, and mucoepidermoid subtypes [52]. Half of patients present with localized disease, the rest with regional nodal or distant metastases. A strong causal relationship exists between oncogenic strains of HPV (types 16 and 18) and SCC. Anal intraepithelial neoplasias (high grade, low grade) are precursors of SCC [52]. Most patients with anal canal cancers present with a slow-growing intra-anal or perianal mass, bleeding, 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 lymphadenopathy. Chemotherapy (mitomycin-C and 5-fluorouracil) and radiation are the recommended treatment modalities for both the anal canal primary and inguinal disease; small superficial lesions may be excised. 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. 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

Introduction

Colorectal cancer (CRC) is currently the third ranked cancer in terms of morbidity and mortality in the United States [1]. There were 102,480 new cases in 2013 alone, with 50,830 deaths which affected 9 % of the US population of that same year [1]. CRC affects men and women equally with the probability of developing invasive CRC being roughly 1 in 19 over the average American male's lifetime and 1 in 21 for females, with 90 % of those cases in both sexes after age 50 [1]. This has significantly changed over the last 25 years with a 30 % decrease in the incidence and mortality from the 1980s due to multiple factors [1]. The highest mortality rates remain among African Americans (49.6 per 100,000) compared to Caucasians (33.1 per 100,000) [1]. The lowest incidence rates are found in the Asian American and Pacific Islander populations (73.5 per 100,000) [1]. The cost of care is also staggering with $14 billion spent in 2010 alone and projected costs to rise 20 % by 2020 [2]. Even with the significant decrease in incidence and death over the last 25 years, the projected increase in cost is 20 % by 2020, and this is without the assumption that an aging population will result in an increase in the number of people over age 50 as the baby boomers age [2].

Americans have a 5 % chance over their lifetime of developing CRC based on the most current population data. CRC has an insidious, and sometimes asymptomatic, presentation which necessitates a good routine screening policy in the healthcare system especially as this is the best prevention modality when compared to all other risk factor adjustments. There are multiple risk factors including polyps, genetic predisposition, diet, medications, social habits, and other associated conditions which can increase the risk of CRC. Multiple diagnostic and screening modalities are available, and these can be tailored based on the patient, resources available, and the provider's abilities to do in-office procedures. Colonoscopy and flexible sigmoidoscopy are procedures that family medicine doctors can learn and then provide for their patients if they so desire. Once CRC has been diagnosed, surgery is the generally best used treatment modality, and if found early, the prognosis for CRC remains positive overall.

Presentation

One of the major challenges of CRC is the appropriate diagnosis, especially as symptoms may be mild or the patient may be completely asymptomatic. Anemia is the most common presenting sign, 51 % of cases, for those with CRC [3]. Those with lower grade tumors were less likely to have anemia (29 %) compared to those with higher grade tumors (59 %) [3]. However, as anemia is the most common sign of CRC, then all males with anemia and all post-menopausal females with anemia should always be evaluated for CRC. Beyond anemia, 66 % of patients have GI symptoms and 25 % have nonspecific symptoms (Table 1) [3]. Patients with symptoms are often symptomatic for an average of 14 weeks, but there is no association between duration and stage of CRC [4]. For specific sites, distal cancers involving the rectum, sigmoid, and descending colon are associated more commonly with rectal bleeding (OR 3.45; 95 % CI 1.71–6.95), constipation (OR 3.16; 95 % CI 1.38–7.24), and anemia (OR 1.34; 95 % CI

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Table 1 Most common primary symptoms for patients presenting with a new diagnosis of CRC

Hematochezia – 33.7 %
Abdominal pain – 22.3 %
Weight loss – 5.6 %
Weakness – 4.8 %
Obstruction – 4.4 %
Perforation – 1.2 %

1.16–1.54) [4]. Proximal cancers are more likely to involve nonspecific GI symptoms such as abdominal pain, weight loss, and weakness which is why a thorough history involving familial CRC and personal screening is imperative in these nonspecific cases.

It is important to note that 12 % of patients presented with CRC without any active symptoms [3]. In these cases, metastasis or perforation may be the most common presenting factor with CRC. For metastatic disease, the initial location of the cancer determines location due to blood and lymphatic flow from various sections of the colon. Colon cancer is more likely to metastasize the liver and lung, and rectal cancer is more likely to metastasize to the lung and bone [4]. Lytic or other lesions in these cases should prompt the provider to ensure that a patient's CRC screening is up to date. Patients can present with obstruction or perforation as an initial symptom of CRC, with large bowel perforation very suggestive of CRC [5]. Those who present with an emergent condition, usually obstruction and/or perforation, have a poorer prognosis compared to other patients with CRC with a hazard ratio (HR) of 1.68 (95 % CI 1.49–1.90) and to those undergoing elective surgery [5]. This makes clinical sense as emergency surgery in general has more risk than planned, and perforation means that the surgeons will be working with a non-sterile cavity which is certainly more prone to infection.

Risk Factors

Polyps

Polyps, or adenomas, are one of the single most important risk factors for the development of CRC with the greatest risk found in those polyps that are largest. Various examples of polyps are shown below in Fig. 1, and overall they are an example of what is found on colonoscopy and flexible sigmoidoscopy. Historically, for adenomas measured in vivo, a single polyp greater than 1 cm has a relative risk (RR) of 3.5 (95 % CI 2.4–5) for developing CRC compared to an RR of 6.5 (95 % CI 3.3–11.8) for those who have multiple polyps $\geq$ 1 cm [6]. The 1 cm measurement is based on the colonoscopist visual evaluation and measurement which is often confirmed with the samples returned to pathology. In comparison, small tubular adenomas, defined as $<$ 1 cm, had no statistically significant increase if the patient only had 1–2 of these sizes of polyps (95 % CI 0.1–1.3) [6]. Loberg et. al looked at the actual versus expected mortality for CRC in 2014 by showing that those with small polyps, $<$ 1 cm, had an SMR (standardized mortality ratio) of 0.75 (95 % CI 0.63–0.88) compared to larger adenomas which were associated with a higher mortality SMR of 1.16 (95 % CI 1.02–1.31) [7]. Other associated risks for polyps include those that are of high grade, such as tubulovillous or tubular adenoma with high-grade dysplasia. Any patient with high-risk polyps should notify their immediate family as this can affect their screening (as described in the screening section below).

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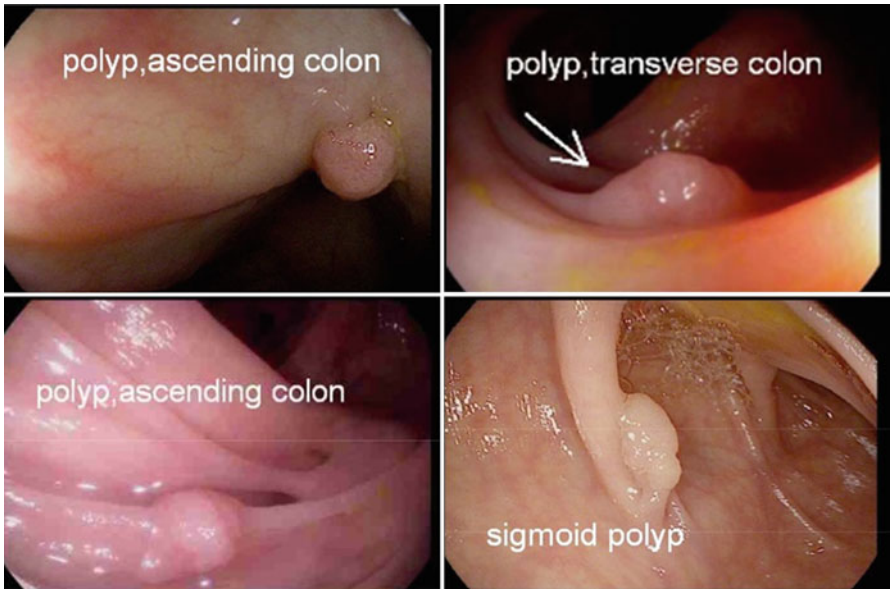

Fig. 1 Various examples of polyps seen on colonoscopy

Genetics

Genetics are the second most significant CRC risk factor behind high-risk adenomas. CRC risk is elevated in first-degree relatives of those with large adenomas, RR 1.35 (95 % CI 1.25–1.46), and those with advanced adenomas, RR 1.68 (95 % CI 1.29–2.18), compared with control cases [8]. Other studies show that the risk for CRC, or high-risk adenomas, is RR of 4.36 (95 % CI 1.60–10.21) in first-degree relatives compared to those without any family history [9]. The two most specific genetic conditions are familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC) or Lynch syndrome. FAP affects 1 in 10,000 births and is associated with an increased burden of polyps, sometimes >100, and CRC on average by age 39 [10]. Hereditary nonpolyposis colorectal cancer (HNPCC), or Lynch syndrome, is more rare than FAP but still has an average CRC diagnosis at age 45 [10]. Whereas FAP is due to loss of function of cancer regulation APC gene and has a large polyp burden, HNPCC is due to a mutation in the "housekeeper" genes and is associated with less polyp burden during colonoscopy [11]. Both of these conditions require more aggressive screening than usual risk patients and should be sent to gastroenterology for evaluation with possible genetic screening.

Diet

Many patients would like to know what diet changes they can make in order to decrease their risk of colorectal cancer. Multiple diets including vegetarian, low red meat, Western, Mediterranean, and supplements have been evaluated with mixed results. Koushik et. al in a 14-study meta-analysis in 2005 showed that there was no significant overall decrease of overall CRC for diets with increased fruits/vegetables (RR 0.91; 95 % CI 0.82–1.01) [12]. However, when specific CRC site was evaluated, diets high in fruits/vegetables (>800 gm/day) was associated with a statistically significant decrease for distal CRC (RR 0.74; 95 % CI 0.57–0.95) compared to proximal CRC (RR 1.02; 95 % CI 0.82–1.27) [12]. Diets high in processed meat, defined as the highest tetrile compared to the lowest tetrile, had a higher risk of CRC compared to other categories (RR 1.5; 95 % CI 1.04–2.17) [13]. High consumption of red meat was also associated with higher risk of rectal cancer (RR 1.71; 95 % CI 1.15–2.52) [13]. This data is limited by confounding factors but it is reasonable to educate patients that diets low in processed/red meats and high in fruits and vegetables may be healthy options for the prevention of CRC besides the

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other positive health implications in these diets. In other meats, long-term consumption of fish and poultry was inversely related to CRC but not statistically significant (RR 0.84; 95 % CI 0.7–1.02) [13]. Beyond meats and vegetables, diets high in calcium and dairy products, highest quintile compared to the lowest, are also inversely associated with colorectal cancers (RR 0.79; CI 95 % 0.7–0.89) [14]. However, at this time there is not one specific "CRC prevention diet," and patients should be educated on the facts and allowed to make their own decisions regarding their diets.

Medications

Besides diet, medications have been evaluated for either the prevention or association with CRC. Daily use of aspirin is associated with a significant reduction in the incidence of adenomas in controlled trials (RR 0.82; 95 % 0.7 −0.95) and a 22 % reduction in the incidence of CRC in cohort studies [15]. Furthermore, in those diagnosed with CRC, regular use of aspirin is associated with decreased incidence of distant metastasis (OR 0.69; 95 % CI 0.57–0.83) but did not have any significant reduction for local/regional spread (OR 0.98; 95 % CI 0.88–1.09) which is consistent with other RCTs [16]. Currently, the USPSTF recommended against (D recommendation) using ASA or NSAIDs for the prevention of CRC [16]. It should be noted that as of fall 2014, this data is under review, and the USPSTF is looking at their recommendations regarding ASA and CRC, but this review will take some time. Supplements are also pushed in media and advertisements for colon health, and this has been evaluated in a few studies. Meta-analysis has shown that each 10-nmol/L increase in blood 0,25-(OH) vitamin D is associated with a 6 % reduction in risk for CRC (95 % CI 3–9 %), but the USPSTF states that there is not enough evidence to recommend Vitamin D supplementation for the prevention of cancer (I recommendation) [17, 18].

Social

Obesity is a risk factor for CRC. Each 5 kg increase in abdominal body fat for men is associated with a 22 % increase in the incidence of CRC in men and a 9 % increase in the incidence for women (RR 1.24; 95 % CI 1.2–1.28) [19]. There is no data published about the time when this fat places the patient at risk or if weight loss during a given time reduces the risk, but healthy weight should be encouraged, and stressing cancer reduction may help patients (among the plethora of other health benefits). Other lifestyle choices such as tobacco use and alcohol are also important risk factors for CRC. Smoking was associated with an increased risk in high-risk adenomas with current smokers having an increased risk (RR 2.14; 95 % CI 1.86–2.46) compared to former smokers (RR 1.82; 95 % CI 1.65–2) [20]. Alcohol consumption was also associated with an increased risk for CRC with heavy drinking (RR 1.21; 95 % CI 1.13–1.28) associated with a higher risk than moderate (RR 1.52; 95 % CI 1.27–1.81) [21]. These diet factors are consistent with the healthy weight, no smoking, and low alcohol consumption recommendations that are already made by family medicine providers.

Associated Conditions

Ulcerative colitis (UC) is a type of inflammatory bowel disease that affects the lining of the colon, and historically, UC was associated with a pooled standardized incidence ratio (SIR) of 5.7 (95 % CI 4.6–7) [22]. Observed over time, the risk of developing CRC for those with UC is 2 % at 10 years (of active disease), 8 % at 20 years, and 18 % at 30 years with all values irrespective of disease extent [22]. However, recent data from Western societies shows that over the last 20 years, CRC incidence associated with UC has been on the decline either due to a steady/declining incidence of UC or due to improved screening

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[23]. This data only applies to Western societies as UC in other regions of the globe is either increasing or those specific countries do not have regular screening for CRC. Other associated conditions such as abdominal radiation as a child is also associated with an increased SIR of CRC as an adult (IR 4.2; 95 % CI 2.8–6.3) [24]. These two conditions are important in the overall health review of the patient and should be considered when discussing their risk for CRC.

Pathogenesis

There are two main pathways for non-syndrome CRC that are important in the pathogenesis: the sporadic and the serrated pathways. The sporadic pathway for CRC is associated with multiple chromosomal segment deletions with a loss of heterozygosity (LOH), with 17p, 18q, and 5q being the most common mutations [11]. The genetic model for CRC is thought to be that adenomas form when normal mechanisms which regulate epithelial renewal are disturbed [25]. Normal intestinal cells have a high turnover due to apoptosis and exfoliation, with proliferation of cells occurring extensively at the crypt base [25]. Mutations in the APC gene, a tumor suppression gene, tend to happen first, and then p53 tumor suppression gene mutations happen later in the formation of the adenoma [25]. In CRC, 75 % had LOH on the 17p chromosome which is associated with the p53 gene [11]. New cellular data has also shown that besides the chromosomal instabilities, sporadic CRC is associated also with a mutation in the KRAS gene; as this gene is basically the molecular "on/off" switch, mutations in this gene are associated with continued proliferation of cells which then lead to cancer [26]. These mutations cause rapid proliferation of the cells and nucleus changes which are consistent with cancer in general.

The second significant pathway, or serrated pathway, involves DNA hypomethylation which suppresses the expression of certain genes and causes mutations in the gene responsible for directing cell growth, the BRAF gene [11]. These polyps are more common in the proximal colon and lack the classic features of dysplasia seen in typical adenomas [11]. There are nonnuclear changes in the histology of serrated adenomas which look more like the "hyperplastic" or benign polyps, and therefore, an accurate pathology diagnosis is paramount [11]. Unlike traditional adenomas, serrated adenomas are due to microsatellite instabilities and mutations in the BRAF gene but not the KRAS gene [26]. Serrated polyps are associated with the Serrate polyposis syndrome which requires at least 1 of the following criteria: (1) at least 5 serrated polyps proximal to sigmoid, with 2 or more $\geq$10 mm; (2) any serrated polyps with a family history of serrate polyposis syndrome; or (3) $>$20 serrated polyps of any size throughout the colon [27]. As discussed below in the screening, these polyps have increased risk of developing into CRC compared to hyperplastic polyps and require increased surveillance.

Diagnosis and Screening

As noted previously, screening for CRC has been paramount for the 30 % decrease in the incidence of CRC over the last 25 years. The Multi-Society Task Force on Colorectal Cancer (MSTFCC) 2008 guidelines for screening methods and timeframes are listed below in Table 2 with the most specific testing being colonoscopy [28]. Colonoscopy is considered the "gold standard" for screening procedures as it reviews the entire colon and is both diagnostic and therapeutic compared to other testing modalities [28]. Furthermore, if any of the other tests are positive, then a full colonoscopy is recommended to evaluate and treat any polyps or CRC noted on the study [28]. Although the MSTFCC recommends all modalities below, it is important to note that the US Preventive Services Task Force (USPSTF) does not

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Table 2 2008 Multi-Society Task Force on Colorectal Cancer (MSTFCC) guidelines for CRC screening methods and recommended timeframes

Study	Timeframe	Diagnostic	Therapeutic
Colonoscopy	10 years	Yes	Yes
Flexible sigmoidoscopy	5 years[a]	Yes	Yes
Double contrast barium enema	5 years[b]	Yes	No
CT colonoscopy[c]	5 years[b]	Yes	No
Fecal DNA testing[c, d]	3 years	Yes	No
Fecal immunochemical testing (FIT)	Yearly	Yes	No
Fecal occult blood testing (FOBT)	Yearly	Yes	No

[a]FOBT recommended at the same time
[b]Bowel prep is still required
[c]The USPSTF rates these as "I" level recommendations as per their guidelines. There is insufficient evidence to asses for the benefits and harms of these modalities
[d]Newly FDA approved with every 3 years as the initial recommendation with limited data [32]

recommend CT colonoscopy or fecal DNA testing as there is not enough evidence regarding the benefits and harms of this practice [18].

The USPSTF recommends screening for colorectal cancer in all normal risk adults beginning at age 50 and continuing until the age of 75 (A recommendation) [18]. They recommend against routine screening in those 75–85, but this should be considered in the totality of the patients' health status including life expectancy and other comorbid conditions (C recommendation) [18]. As of this time, the USPSTF recommends against screening for CRC in any adult over the age of 85 (D recommendation) [18]. The MSTFCC agrees with the USPSTF findings, with the American College of Gastroenterology also recommending that African Americans start screening at age 45 [29]. For those individuals with increased risk of CRC, single first-degree or two second-degree relatives with a diagnosis of CRC or advanced adenoma, the MSTFCC recommends screening at 10 years before the family member was diagnosed, or by age 50 depending on which comes first [28, 29]. An advanced adenoma is considered $\geq$1 cm in size, or with villous elements or high-grade dysplasia [29]. Patients with a personal or family history of FAP/HNPCC have different evaluation schedules, and family medicine providers should consider sending these patients to gastroenterology for a consultation [29].

After the procedure is performed, the follow-up depends on the findings of the initial baseline colonoscopy, outlined in Table 3 below [27]. In those individuals with family history who have a normal initial colonoscopy, they should have continued screening every 5 years per routine instead of the normal 10 years for average risk adults [18, 27, 29]. If the polyp surveillance colonoscopy, listed in Table 3, is negative, then the MSTFCC recommends a return to the 10-year surveillance for average risk adults [18]. Diagnosis is based on pathology results and patients should be notified of their results and the appropriate follow-up interval.

Procedures

Endoscopy

The two options for endoscopy are flexible sigmoidoscopy and colonoscopy, which both can be performed by family medicine providers. Colonoscopy has a low-risk profile with a perforation being one of the most feared complications, but only happening in 0.6 per 1,000 cases [28]. The patient should be aware that perforation may require surgery, admission to the hospital, and antibiotics and, in some cases, may result in patient death. Other serious complications, most commonly bleeding requiring hospital admission or transfusion, are also rare and only occur in 25 per 1,000 cases [28]. However,

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Table 3 2012 recommendations for surveillance and screening intervals for average risk patients

Baseline colonoscopy findings	Recommended surveillance interval (years)
No polyps	10
Small (<10 mm) hyperplastic polyps in the left colon	10
1–2 small (<10 mm) tubular adenomas (TA)	5–10
3–10 tubular adenomas	3
More than 10 small TAs	<3
One or more large (≥10 mm) TA(s)	3
One or more villous adenomas	3
Adenoma with high-grade dysplasia	3
Sessile serrated (SSA) polyp(s) < 10 mm with no dysplasia	5
SSA polyp ≥10 mm, or those with dysplasia	3
Serrated polyposis syndrome	1
Piecemeal removal of a ≥10 mm TA	6 months to ensure complete removal

colonoscopy is very effective at finding polyps with miss rates of only 2.1 % for ≥10 mm polyps (85 % CI 0.3–7.3 %), 13 % for 5–10 mm polyps (95 % CI 8–18 %), and 26 % for adenomas 1–5 mm (95 % CI 27–35 %) [30]. Although the miss rates seem large for the very small polyps, the clinically significant large polyps which are more likely to become CRC have a very low miss rate [6]. Flexible sigmoidoscopy, known as "flex sig," is a shorter version of colonoscopy which only goes to the splenic flexure and must be combined with FOBT/FIT in order to have a satisfactory procedure [28]. Flex sig is technically easier to perform and requires less of a bowel prep, usually an enema, and it is usually covered by insurance plans. A positive flex sig or concurrent FOBT/FIT normally indicates recommendation for a full colonoscopy especially for high-risk polyps.

For any provider doing colonoscopy, there are specific recommended quality markers which include (1) a screening colonoscopy adenoma detection rate (ADR) >15 % for females and >25 % for males, (2) a ≥7 min withdrawal time, and (3) a 95 % cecal intubation rate for screening colonoscopies [31]. ADR is one of the best outcomes-based markers as ADR is inversely proportional with the risk of interval CRC with pooled (male and female) ADRs >28.41 % associated with a hazard risk of 0.70 of interval CRC (95 % CI 0.54–0.91) [32]. Also, even though >6 min withdrawal time is associated with a quality procedure, those providers with ≥10 min of withdrawal time is associated with a better ADR overall [31]. These metrics should be tracked in order to help with credentialing and ensure that all endoscopists are meeting their quality indicators.

Fecal Screening

Various types of fecal testing are available for primary care to include fecal occult blood testing (FOBT), fecal immunochemical testing (FIT), and fecal DNA. FOBT is highly sensitive, but not very specific, as it looks for heme in the stool when combined with hydrogen peroxide based on a peroxidase-like effect of heme [28]. There can be many false positives including diets high in red meats, medications, and non-lower GI tract bleeding. Other options include the FIT which utilizes specific antibodies to look for globin in the stool [18]. This increased specificity compared to FOBT is due to the test specifically targeting human globin and that globin is normally broken down in the small bowel as compared to heme; this decreases the amount of false positives that can be problematic with FOBT. The newest approved fecal testing is fecal DNA which tests for specific mutations as listed above in pathogenesis. This test has 92 % sensitivity for CRC detection and, like FIT, does not require special diets or medication alterations

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[32]. All of these tests are recommended to be performed as above in Table 3, and patients should be educated that these tests detect large polyps and CRC but are not an actual therapy.

Radiological Screening

Two radiological screening options include double contrast barium enema and CT colonoscopy. Both of these require some bowel preparation, have a very low risk of perforation, and are considered appropriate by MSTFCC screening recommendations [28]. Also for both tests, if 1 or more polyp >6 mm is seen on imaging, then a complete colonoscopy is recommended [28]. These tests do not have to be combined with FOBT/FIT. The double contrast barium enema uses plain film imaging where first barium is passed via a tube to the rectum and then air is passed through that same tube to improve the contrast of the image. CT colonoscopy, or virtual colonoscopy, uses air pumped into the colon as contrast and then uses 3D imaging of the colon to evaluate for CRC and large polyps. As a general rule, neither of these tests requires any significant sedation. These imaging tests can be considered in patients who do not want the sedation required for colonoscopy but want more advanced testing than fecal testing.

Overview of Colonoscopy Procedure

After appropriate informed consent has been obtained, the patient undergoes complete bowel prep the day before the procedure. This usually includes only clear liquids the day before the procedure and then use of a commercially available bowel prep which is usually provider or location dependent. As a general rule, only high-risk groups are given pre-procedure antibiotic prophylaxis which should be decided after reviewing the most up-to-date guidelines published by the American Heart Association. The patient is gowned and placed in the left lateral decubitus position. Sedation, either conscious or complete, is given for analgesic and anxiety control. The provider examines the rectum with a digital exam to evaluate for any masses and ensures that the colonoscopy can pass completely through the rectum. Using a high-definition chromographic colonoscopy, the provider inserts the scope and insufflates either air or CO2 until the lumen becomes apparent. The scope is then passed into the sigmoid colon which is one of the most difficult locations of the procedure. The sigmoid may either have adhesions from prior procedures or have diverticula disease (see Fig. 2). Maneuvers such as rightward torqueing and withdrawing of the scope may be required to reduce loops, and lower left quadrant pressure can be very helpful in splinting the colonoscope to ease movement. The colonoscope continues to be advanced until the cecum is reached and pictures are taken of the appendicle orifice and the terminal ilium. The scope is then withdrawn while maintaining direct visualization of the bowel wall and taking at a minimum 7 min to withdrawal of the colonoscope. Obtain any necessary biopsy noted, and remove any polyps seen with either forceps biopsy or snare. These biopsies and polyps should be sent to a certified pathologist for evaluation, and the colonoscopist should track these on some systems to ensure results were sent to the patient and they can

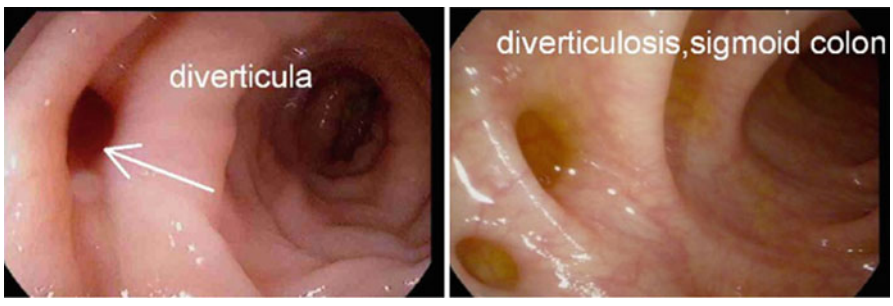

Fig. 2 Various diverticula noted in the sigmoid colon during colonoscopy

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calculate their quality markers. In the rectum, the scope should be retroflexed to evaluate the dentate line for any rectal masses [33].

Treatment

Beyond complete polyp removal during colonoscopy as possible, there are more steps required when dealing with large masses suspected to be CRC. The tumor-node-metastasis (TMN) staging system from the American Joint Committee on Cancer (AJCC) is the current standard for colorectal cancer staging [34]. This scale applies various metrics based on the primary tumor (T), regional lymph nodes affected (N), and distant metastasis (M) [34]. The TMN system is data driven, has a continuous process improvement system, has comprehensive rules to ensure uniform application, and is multidisciplinary in design [34]. Surgery is the primary modality of treatment and staging for cancers of the lower gastrointestinal tract [35]. For early stage cancers, standard resection is the only therapy required for treatment, and this can either be done laparoscopically or via open resection [35]. There are no significant differences in CRC mortality, recurrence, or number of lymph nodes harvested when comparing open versus laparoscopic resection of colorectal cancer [36]. As the stage of tumor increases, the chance of cure with surgery decreases and adjuvant therapies such as chemotherapy and radiation therapy are required to increase the probability of cure in patients with CRC [35].

Chemotherapy agents such as fluoropyrimidine/oxaliplatin are used as first-line agents in 71 % of cases by 2007 with bevacizumab being the other first-line agent option [37]. Patients who were treated in US academic centers are also more likely to receive anti-EGFR monoclonal antibodies, but this has decreased by approximately 18 % recently due to the limited use in patients with KRAS tumors [37]. Chemotherapy and surgery are also useful in metastatic non-resectable CRC as palliative agents which can improve patients' symptoms and extend survival to the point where some oncologists argue that metastatic CRC can be considered "more of a chronic illness than an acutely fatal one" [38].

Imaging has a limited role overall in the diagnosis and management of CRC. CT is recommended as the initial radiological evaluation for staging CRC to assess extent of disease and evaluate metastases to lung and/or liver [39]. Besides initial CT for staging purposes, there are a few other important imaging modalities for CRC. PET-CT is useful for postoperative recurrence of disease and evaluates extra-hepatic disease in high-risk patients [39]. MRI is the recommended methodology for patients with rectal cancer who are candidates for surgery in order to improve local T-staging and N-staging [39].

Prognosis

When found early through appropriate screening modalities, CRC overall has a very good prognosis compared to some other cancers. For all patients with CRC, the overall 5-year survival rate is 65.2 % [40]. Five-year stage-specific survival rates are listed below in Table 4 and are based on the 6th edition of the American Joint Committee on Cancer (AJCC) published in 2004 [40]. Based on the TMN stage, it is clear that tumors that invade other organs locally and/or distant metastasis carry with them a worse prognosis than localized tumors.

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Table 4 2004 American Joint Committee on Cancer (AJCC) stage specific survival rates for CRC

AJCC stage	T stage	N stage	M stage	5-year survival rate (%)
I	T1 or T2	N0	M0	93.2
IIa	T3	N0	M0	84.7
IIb	T4	N0	M0	72.2
IIIa	T1 or T2	N1	M0	83.4
IIIb	T3 or T4	N1	M0	64.1
IIIc	Any T	N2	M0	44.3
IV	Any T	Any N	M1	8.1

T1 tumor involves submucosa, *T2* tumor involves muscularis propria, *T3* tumor invades through the muscularis propria into the subserosa or into nonperitonealized pericolic tissues, *T4* tumor invades other organs or structures and/or perforates viseceral peritoneum, *N0* no regional lymph node metastasis, *N1* metastasis to one to three regional lymph nodes, *N2* metastasis to four or more regional lymph nodes, *M0* no distant metastasis, *M1* distant metastasis [40]

Prevention

The best prevention for the development of CRC is screening. As previously listed, incidence of CRC has decreased by 30 %, and survival has improved by 30 % over the last 25 years which is most likely due to improved screening and treatment with colonoscopy during the precancerous polyp stage [1, 6, 7]. Looking at the 2006 annual report on CRC addressing the impacts of screening, it has been shown that nearly half of the 30 % decrease is from screening and treatment of precancerous polyps [41]. This is one of the reasons that it is imperative to encourage screening in the patient population which is consistent with the strong recommendation from the MSTFCC and with the A level recommendation from USPSTF [18, 28]. Based on the data available, without a doubt, it can be stated that "screening for colorectal cancer saves lives" which is impressive given the multitude of other cancer screening tests that have fallen out of favor or have decreased the aggressiveness of surveillance.

Other prevention options as discussed above do not have strong recommendations. Currently, the USPSTF does not recommend ASA/NSAIDs, calcium supplementation, or vitamin D supplementation for the prevention of CRC [16–18]. There are studies that address diet and CRC, as listed above in the diet section under risk factors, and these diets can be considered for those patients who want to aggressively decrease their risk of CRC, but they are not recommended as a panacea for prevention for CRC. However, due to the other positive health considerations, a proper balanced diet should be recommended by the family medicine provider. Many studies are continually ongoing regarding these prevention factors, and all providers know that recommendations change over time.

Family and Community Issues

Outside of the support for those with CRC, one of the best things families can do is to encourage their spouses and other loved ones to get a screening colonoscopy. Although there may be a stigma associated with this test, open conversations with those patients who are old enough to get a screening colonoscopy should be performed by the family medicine doctor. For those patients who do not wish to undergo

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invasive screening, then fecal studies are appropriate. For community aspects, besides the overwhelming financial costs, support and awareness of CRC and screening options are paramount [2]. These can include options from education campaigns on various media and social media sites to ensure that all insurance plans include reasonable screening options for CRC.

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Family Medicine
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Surgical Problems of the Digestive System

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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) 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 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, following trauma) 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

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analgesics. *Rigidity* is the involuntary contraction of abdominal wall muscles that resolves only after anesthesia. "*Rebound tenderness*" is worsening of 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 core 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 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. Post-operative 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 child-bearing age may indicate pregnancy. Many features of abdominal pathology (nausea, vomiting, constipation, dysuria, pelvic/abdominal discomfort) are features of normal pregnancy. Medications (anti-arrhythmics, nonsteroidal anti-inflammatory agents – NSAIDs, steroids, beta-blockers, anticoagulants, and over-the-counter medications and supplements) often contribute 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

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progression. Elderly patients are usually on multiple medications (beta-blockers, NSAIDs, anticoagulants, narcotics, antidepressants) all of which contribute to modify 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 evaluating acute abdomen.

A systematic approach (inspection, auscultation, palpation, and percussion) is recommended. All hernial orifices (umbilical, inguinal femoral) and 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). Reexamination enables the provider to detect evolving pathology. Palpatory signs consistent with specific pathology (Murphy's sign in cholecystitis or Rovsing's sign in appendicitis) may be detected. Percussion is useful to detect free fluid, gaseous distention, and rebound tenderness. Auscultation detects abnormal bruits and borborygmi (peristaltic sounds); increased 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 supine patients, the right hip should be elevated slightly 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 (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, 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, measurement of cardiac enzymes, or D-dimer levels.

Age, pregnant state, medications, and preexisting 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 recommended 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.

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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)
[b]Computed tomography – using oral/rectal and intravenous contrast

Table 2 Special diagnostic studies in patients presenting with an acute abdomen

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

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) 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].

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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 pre-operative testing should be based on the need to clarify and optimize the patient's physical status and monitor resuscitation and recovery. Patients who have been assessed and determined to have no preoperative indication for laboratory tests can safely undergo surgery with tests drawn only as indicated during or after surgery. Tests should be ordered only when initial evaluation would have indicated the need for the test even if surgery had not been planned.

Resuscitation

Resuscitation commences with evaluation and optimization of airway, breathing and circulation and should precede diagnostic imaging. Cerebral hypoperfusion and mental status changes increase risk of aspiration. Presence of pallor, cyanosis, mottling, prostration, hypotension and tachycardia in addition to confusion suggest sepsis and dehydration, or ongoing bleeding. Multiple studies have shown that early administration of analgesia does not interfere with subsequent ability to diagnose and treat acute abdominal pathology, nor does it impact outcome [2]. Antibiotics are not administered in stable and immunocompetent patients unless an infective source is evident or identified; immunocompromised patients require early and pre-operative 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 emergency surgery is indicated for continued bleeding or progressing sepsis. It is important to recognize need for transfusion, identify and treat life-threatening causes of acute abdominal pain and continue to 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. Pre-operative 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 re-established.

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

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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]

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 findings, hypotension, prostration
Myocardial infarction	Upper abdominal pain, tachycardia, hypotension, minimal abdominal findings

Text from multiple sources

injury. 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 recommended [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 visits with abdominal pain in children include constipation, Henoch-Schonlein purpura, pneumonia, streptococcal infection (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].

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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 usually involve multiple organs 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 damaged in children [17].

Diagnosis

Patients with BAT may present a difficult 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, mental status changes, and drug and alcohol use. Physical examination should comprise 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 evaluated 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 femur fracture also have high specificity for intra-abdominal injuries [20]. However, physical examination is only 55–65 % sensitive in BAT [17].

Management

Initial management should optimize patient's airway, breathing, and circulation. Laboratory analysis should focus on documenting patient 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-abdominal injury [20]. Adequate intravenous access (two large-bore peripheral lines or central venous access) is obtained, a nasogastric tube is inserted to decompress the proximal bowel and a Foley catheter is placed to monitor urine output.

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In hemodynamically unstable patients (systolic blood pressure ≤90 mmHg) with BAT, bedside ultrasound (FAST – 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 significant trauma to other systems (thorax, cranium, pelvis, long bones) requiring surgical intervention and equivocal abdominal findings. DPL does not identify the source of bleeding or retroperitoneal injuries. Prior abdominal surgery, obesity, hepatic cirrhosis, pregnancy and coagulopathy are contraindications. It has largely been superseded by FAST in unstable patients and 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 ≥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.

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

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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 presence of 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 intra-colonic air producing greater pressure over the inflamed appendix, worsening the pain (Rovsing's sign). 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) 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, useful 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 less, 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 result of imaging, should undergo surgery, or observation until the clinical picture becomes clearer [28].

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.

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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 post-operative 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 intra-operative 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 lead to miscarriage or pre-term 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 non-operatively 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 presenting problem in the adult and 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, lower alcohol consumption, 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 requiring intervention.

Gallstones may cause functional dyspepsia, biliary colic, acute cholecystitis, mucocele of the 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

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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 poly-microbial 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 (three-fold) 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 co-exist [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 immnucompromised 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 single or combination of laboratory abnormalities is either sufficiently sensitive or specific for cholecystitis. Leukocytosis with bandemia, elevations of serum bilirubin, and liver enzymes are seen, 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 ruling in or out 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.

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, as rapid disease progression and greater risk of complications (gangrene, emphysematous cholecystitis, empyema, or rupture) are more likely in this subset [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 returns 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]. Ill patients, 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 initial decision to perform open cholecystectomy or greater risk of conversion [36].

Acalculous Cholecystitis

Acalculous cholecystitis usually follows major trauma or surgery, resuscitation from cardiac arrest, systemic sepsis or major co-morbidities such as congestive heart failure, end-stage renal disease and cancer [37]. Delayed diagnosis, poor patient status and increased complications (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].

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Special Situations

Conservative management of acute cholecystitis is recommended in pregnancy unless pancreatitis, ascending cholangitis, or common bile duct obstruction develops. Surgery is indicated in failure to respond to conservative measures. 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, no 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.

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 comprise the majority (75 %) [40]. Other commonly occurring hernias include umbilical, paraumbilical, and incisional hernias; the rest (femoral, epigastric, spigelian, lumbar, gluteal, sciatic) 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.

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 contents of the hernia sac can be myriad – 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). Oemntum 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

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 a bulge in the groin that is progressing. 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 standing 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 differentiate indirect, 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 groin lump does not reduce spontaneously in the recumbent position, or on attempts at reduction. Patients with obstructed hernias present with features of small 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 hernial contents (rare – 0.55 % of asymptomatic hernias followed over 4 years) [43]. Imaging studies (US, CT) are useful to confirm the diagnosis and document coexisting problems

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(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].

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 nonabsorbable 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 nonmesh 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 diagnosis of hernia, visualization of the defect and hernial sac, small incisions, and rapid return to work [47]. Disadvantages include need for general anesthesia and mesh, contributing to increased direct costs. Antibiotics are not indicated in elective hernia repairs.

Surgical techniques in irreducible and obstructed hernias are no different except that patients with bowel obstruction need bowel rest, nasogastric suction, and replacement of fluids and electrolytes, which is continued until return of bowel function. Strangulated hernias with ischemic contents require resection of the contents (omentum, bowel). 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 complication. 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 [47, 48].

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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 [49]. 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 %) [50]. 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 [51]. 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) [51]. 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 in esophageal, gastric outlet and high SBO, central in low SBO, and generalized in LBO [51, 52]. Constipation may be absent initially in bowel

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)

Text from multiple sources

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obstruction due to continued peristaltic activity distal to the obstruction [52]. 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). High white count is also a feature of peritonitis and sepsis. Elevated lactic acid and metabolic acidosis suggest gangrene, peritonitis, and sepsis [53].

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 produces a "stepladder" pattern of air-fluid levels within bowel loops on erect abdominal x-rays. Presence of differential air-fluid levels in the same loop of and a mean air-fluid level width of at least 25 mm is very characteristic of high-grade SBO [54]. On supine abdominal x-rays, distended jejunal (small bowel folds traversing the length of the lumen – valvulae conniventes) and ileal loops (featureless) are seen. With colonic obstruction, distended colon (haustral folds, not traversing the length 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) [54]. 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 worsen intravascular volume depletion 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) [51]. CT also helps identify those patients without initial clear indications for urgent surgery, likely to fail conservative management and benefiting from early intervention. By incorporating clinical, laboratory, and CT findings 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), Schwenter et al. 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 [55]. Bedside US is an option in unstable patients and during 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 [56]. Colonoscopy is useful in confirming the diagnosis of LBO

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when in doubt, obtaining biopsies of obstructing lesions, derotating sigmoid volvulus, decompressing pseudo-obstruction, stenting strictures, and avoiding unnecessary surgery [57].

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 necessity for urgent surgery. Early surgery is required after resuscitation in patients with frank peritonitis, 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 improvement (optimal duration of conservative management is controversial) and if progressive clinical instability and acidosis indicate worsening ischemia or sepsis develop. Presence of 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 contamination, the healthy bowel ends are sutured to the skin (jejunostomy, ileostomy, colostomy); the ends reanastomosed 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 ($<4{,}500/mm^3$), renal dysfunction (creatinine >1.2 mg/dL), and low functional status. Wound contamination or infection and resection of bowel also predict increased postoperative morbidity [58]. Risk of death is lower (2–8 %). Advanced age, higher ASA class (≥ 3), chronic illness, treatment delay, and bowel ischemia predict higher mortality [51].

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.

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 [59] Incidental cholecystectomy is recommended in patients prone to develop cholelithiasis and cholecystitis (hemolytic disorders, gall bladder polyps and cholesterolosis, Porcelain gallbladder and during gastric bypass surgery) [60] 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, omental interposition between the abdominal wall and intra-abdominal organs, and excluding foreign materials in the peritoneal cavity (sutures) help.

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Family Medicine
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Selected Disorders of the Digestive System

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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 USA 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 USA include enterohemorrhagic *E. coli*, *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., 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)?

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 compared to lactoferrin which is >90 % and >70 %, respectively [5]. Positive occult blood in combination with lactoferrin increases the likelihood of an

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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
Clostridium difficile	Hospital admission, antibiotics within past 3 months	+/− fever, +/− abdominal pain, +/− bloody stools	Metronidazole 500 mg tid x 10 days; oral vancomycin 125 mg qid x 10 days if severe
EHEC	Consumption of raw beef, seed sprouts, raw milk	No fever, abdominal pain, bloody stool	Oral/intravenous hydration

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 *Clostridium 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), community waterborne outbreaks, children attending daycare, or recent travel to mountainous regions [7].

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.

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 produce, 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

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cautioned against as their use may increase risk of developing hemolytic uremic syndrome (HUS) in which the patient develops thrombocytopenia, hemolytic anemia, and renal failure [8].

Clostridium difficile

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 is to stop the offending antibiotic if possible and introduce therapy with metronidazole 500 mg tid for 10 days for mild to moderate cases. Oral vancomycin 125 mg qid for 10 days is 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 such as alcoholism, and people with chronic liver disease are at risk for contracting *Vibrio vulnificus* from shellfish, and 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].

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Diagnosis

There is no one single plasma marker sensitive enough to make an early diagnosis [10]. Significant leukocytosis may be the only initial lab abnormality with white blood cell counts often exceeding 20,000 cmm [12]. 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].

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 availability of CT scans for acute ischemia but still may have high utility in the workup of chronic mesenteric ischemia [11].

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

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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 often occurring in patients older than 60 years of age with a predilection for affecting women threefold more than men [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 of dissection with prior angioplasty attempts [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 hypercoaguability should be advised on risks of medications which 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 USA 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 USA [14].

Multiple risk factors are associated with influence on 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 soya is common whereas allergies to peanut, tree nuts, fish, and shellfish tend to persist.

Table 2 Risk factors for food allergy

Male gender (in children)
Asian/Black ethnicity
Atopic dermatitis
Vitamin D deficiency
Reduced consumption of dietary fat
Reduced consumption of antioxidants
Obesity
Increased hygiene

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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 which 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 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 where epinephrine was required in only 2 % of in-office oral food challenges [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]. Despite recommendations for exclusive breastfeeding to reduce atopic disease, there is conflicting data with one study of over 50,000 school-age children showing a greater tendency of eczema in the children who have ever breastfed [14]. 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].

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Table 3 Acquired conditions that may contribute to lactose malabsorption

Small bowel bacterial overgrowth (SBBO)
Infectious enteritis (giardiasis)
Celiac disease
Inflammatory bowel disease
Medications
Gastrointestinal surgery
Short bowel syndrome
Radiation enteritis

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. There is an ethnic predilection due to non-persistence of the lactase enzyme affecting 5–20 % of Caucasians, 60–80 % of East Indians, 70 % of Latinos, 70 % of African Americans, and >90 % of Southeast Asians [17]. It is also important to point out that lactase deficiency may be secondary to another acquired condition such as those listed in Table 3.

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 tolerance 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 testings. Genetic testing for the -13910*T genotype which evaluates for lactase non-persistence 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 [17].

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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. 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 1,200 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 (paresthesias 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.

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].

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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 resp failure when severe	0.5–3	East Asia, China, and Japan
Ciguatera	Ciguatoxins	Reef fish	Severe GI effects, myalgia, paresthesia, ataxia, rarely fatal	3–30	All tropical areas
Paralytic shellfish poisoning	Saxitoxin and gonyautoxin	Bivalve shellfish (mussels, oysters, clams)	Descending paralysis, resp failure when severe	0.5–4	NW/NE USA, 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

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 USA 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 a 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 toxin 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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Urinary Tract Infections

The Renal, Urinary, and Male Genital System

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Contents

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Urinary tract infections (UTI) are defined as the presence of significant numbers 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].

Four major risk groups have been identified: school-age girls, young women in their sexually active years (including pregnancy), 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 young men, catheter-associated UTIs, asymptomatic bacteriuria without a catheter, chronic UTI in the elderly, UTIs with spinal cord injuries, and fungal UTIs. 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.

Asymptomatic Bacteriuria

With the exception of pregnancy (see below) 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 infected more often, presumably related to the uncircumcised patients' susceptibility. In neonates the prevalence is threefold higher among premature infants [4]. For girls the incidence steadily rises with a small transient increase at preschool time and then remains level until sexual activity becomes a factor. Asymptomatic bacteriuria is absent in boys until later in adult life when obstructive problems occur. In girls asymptomatic bacteriuria is present early in infancy and remains fairly constant until 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, and lack of circumcision and instrumentation [4]. In children without urinary tract abnormalities, periurethral bacterial colonization is a risk factor for UTI [6].

Escherichia coli accounts for as much as 80 % of cases of UTI [7]. In neonates and complicated cases, *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) [8].

Imaging Evaluation

Imaging tests 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 [8]. Debate continues about the best radiologic approach for evaluating UTI [9]. The issue centers around the role of radionuclide scans and how these methods may replace or be used in conjunction with traditional ultrasonography (US), voiding cystourethrography (VCUG), intravenous pyelography (IVP), and spiral computer-assisted tomography (CT).

Radionuclide cystography, a method using scintigraphic imaging, gives accurate information similar to that of contrast-based VCUG, with the possible advantage of significantly less radiation exposure [10]. The scintigraphic study using 99 m-technetium dimercaptosuccinic acid (DMSA) has become a leading choice for gauging renal function and identifying renal cortical defects. The DMSA scan is a gold standard for diagnosis of acute pyelonephritis; however, it should not be used as first line due to the exposure of radiation, and it is invasive [11]. 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 is strong at ruling out obstruction. The 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 [9].

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 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 [9].

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 and physical examination should include a rectal examination to detect a large fecal reservoir as fecal impaction can obstruct urine flow [12].

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 infection, 7–14 days treatment has been recommended; for uncomplicated infection, 3–5 days is adequate [9].

For uncomplicated UTI, oral agents may include amoxicillin, trimethoprim-sulfamethoxazole, nitrofurantoin, or cephalosporins for a duration of 3–5 days. Antibiotic treatment of asymptomatic bacteriuria in children is controversial based on certain issues: 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 unknown long-term side effects of antibiotics [4]. A reasonable approach with asymptomatic bacteriuria is to treat children younger than 5 years or those who have urinary tract structural abnormalities.

UTIs During Pregnancy

Pregnant women with UTIs are at greater risk of delivering infants with low birth weight, premature infants, preterm infants with low birth weight, and infants small for gestational age. In addition, the likelihood is greater for premature labor, hypertension/preeclampsia, anemia, and chorioamnionitis. There is strong evidence that UTI causes low birth weight through premature delivery rather than growth retardation [13].

The risk of pyelonephritis from antepartum asymptomatic bacteriuria may be as high as 30 %. Identification and eradication reduces this risk to less than 5 %. Antepartum bacteriuria has an estimated prevalence of 2–7 % [14].

An optimal time for screening all pregnancies is at the first prenatal visit. A urinalysis and culture should be obtained. If negative, no further cultures 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 follows.

As in nonpregnant females, *E. coli* is the most common cause of UTI during pregnancy, accounting for more than 80 % of isolates. Other organisms include *Enterobacter* species, *Klebsiella* species, *Proteus* species, enterococci, and *Staphylococcus saprophyticus*.

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 3–7 days is used with antibiotics chosen with safety in mind. There is little support for single-dose therapy. Pyelonephritis is managed the same as in nonpregnant females.

Acute Uncomplicated Lower UTI in Young Women

The risk for UTI is increased by sexual intercourse, delayed postcoital voiding, diaphragm and spermicidal gel, and a history of recurrent UTIs [15]. One of three types of infection can account for these infections: acute cystitis, acute urethritis, or vaginitis [3].

Cystitis pathogens include *E. coli*, *S. saprophyticus*, *Proteus* species, or *Klebsiella* species. Symptoms are abrupt in onset, severe, and usually multiple; they include dysuria, increased frequency, and urgency. Suprapubic pain and tenderness and sometimes low back pain also occur. Pyuria is usually present and occasionally hematuria.

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 usually present.

Vaginitis pathogens include *Candida* species, *Gardnerella*, and *Trichomonas vaginalis.* Symptoms include vaginal discharge or odor, pruritus, dyspareunia, and external dysuria without increased frequency or urgency.

With no complicating clinical factors, reasonable empiric treatment for presumed cystitis, prior to organism identification, is a 3-day regimen of any of the following: oral trimethoprim-sulfamethoxazole (TMP-SMX), ciprofloxacin, or levofloxacin. With the complicating factors of diabetes, symptoms for more than 7 days, recent UTI, use of a diaphragm, or age over 65 years, a 7-day regimen can be considered using these same antibiotics.

Recurrent Infections (Cystitis) in Women

Recurrent cystitis can be termed relapse or reinfection. Relapse is defined as a recurrence within 2 weeks of completing therapy for the same pathogen. Reinfection is defined as a recurrence more than 2 weeks after completing therapy for a different species or strain. The vast majority are due to reinfection. For relapse, efforts should be made to rule out a urologic abnormality and to treat for an extended time, such as 2–6 weeks. For two or fewer 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. This regimen is commonly continued for 3–6 months [16]. If the recurrent UTIs are related to coitus, a single low-dose postcoital treatment may be preferable.

Acute Uncomplicated Pyelonephritis in Young Women

Uncomplicated pyelonephritis exhibits findings suggestive of upper tract parenchymal involvement including 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 or possible urosepsis 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 [17].

Complicated UTIs

Clinically, a complicated UTI may present in the same way as an uncomplicated one. A complicated infection occurs in urinary tracts that have a functional, metabolic, or anatomic derangement predisposing to an infection that is more resistant to typical therapeutic measures.

Characteristic organisms present in complicated urinary tract infections include *E. coli*, *Proteus* species, *Klebsiella* species, *Pseudomonas* species, *Serratia* species, enterococci, and staphylococci. Outpatient management is reasonable for mild to moderate illness without nausea or vomiting. The most effective oral antibiotic treatment is ciprofloxacin or ofloxacin administered for 10-14 days, with ciprofloxacin or ofloxacin being first-line agents. TMP-SMX, amoxicillin, or cefpodoxime could also be used. For severe illness or possible urosepsis, hospitalization is necessary with treatment by parenteral ampicillin/gentamicin, ciprofloxacin, ofloxacin, ceftriaxone, aztreonam, ticarcillin-clavulanate, piperacillin-tazobactam, or imipenem-cilastatin. This regimen should be continued until that patient is afebrile and then may be changed to oral therapy with either TMP-SMX, ciprofloxacin, or ofloxacin for a total of 14–21 days [3].

UTIs in Younger Men

Without underlying structural urologic abnormalities, risk factors for UTIs in young men include homosexuality, lack of circumcision [18], and a sex partner colonized with uropathogens [3].

Management of symptomatic cystitis without obvious complicating factors requires a urine culture to establish the pathogen. This step establishes sensitivity and helps differentiate relapse or reinfection in the event of recurrence. Once the culture is obtained, a 7-day course of TMP-SMX, trimethoprim, or a fluoroquinolone is appropriate.

The traditional approach of undertaking a thorough post-UTI evaluation to rule out a urologic abnormality has been disputed [19, 20]. If pursued in young men who have responded to treatment, the chance of finding a urinary tract defect is low [21].

Catheter-Associated UTIs

Catheter-associated UTI (CAUTI) is the most common acquired infection in long-term-care facilities, and in the intensive care setting, 95 % of nosocomial UTIs are CAUTI [22]. The presence of an indwelling catheter for at least 3 days has been identified as a risk factor for UTI, with a 5–10 % incidence of UTI per day of catheterization, and can be a significant cause of morbidity and mortality in this population.

With short-term catheterization, *E. coli* is the most common organism, followed by *Pseudomonas aeruginosa*, *K. pneumoniae*, *Proteus mirabilis*, *Serratia marcescens*, *Citrobacter* spp., *Staphylococcus epidermidis*, and enterococci [23]. In patients with long-term indwelling catheters, infection may be due to ordinarily nonuropathogenic species such as *Providencia stuartii* or *Morganella morganii.* Yeast may become an isolated pathogen when antibiotics are in use [22, 23].

Treatment in this setting depends on the clinical presentation: baseline prevention, antimicrobials for asymptomatic bacteriuria or symptomatic lower UTI, and antimicrobials for a symptomatic (complicated) upper UTI. Prevention focuses on avoiding catheterization if possible. If catheterization is mandatory, minimize the duration and use a closed drainage system. Short-term use of silver alloy catheters in hospitalized patients reduces the incidence of symptomatic UTI and bacteremia [24]. For short-term catheterization of 3–14 days, daily prophylactic norfloxacin, ciprofloxacin, or amoxicillin has shown benefit [21]. For acquired asymptomatic bacteriuria and symptomatic lower UTI after short-term catheter use, a single dose of TMP-SMX (320–1600 mg) has been shown to be as effective as a 10-day course [25].

Chronic UTIs in the Elderly

Among males the incidence of bacteriuria essentially disappears after infancy and reappears during later adulthood as urinary obstruction due to prostate enlargement becomes prevalent. The incidence of UTI in both sexes steadily rises with age during the elderly years [5]. In addition, other age-related physiologic changes play a role in UTI development including lack of estrogen in women, diminished prostatic secretion in men [26], 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. For nursing homes, *E. coli* remains the most common causative organism with *Enterococcus* being the second most encountered in this population, and *S. saprophyticus* does not occur in this setting. Gram-positive organisms can dominate among men.

The presentation of UTIs among the elderly can be similar to that of younger patients. However, these signs and symptoms can be absent or come to attention as fever of unknown origin, altered mental status (lethargy), gastrointestinal complaints, incontinence, and respiratory symptoms [27]. Urine culture and sensitivity obtained from a catheterized specimen is preferable as the sensitivity of urinalysis is diminished in older adults.

In the elderly, antibiotics require minimal dose adjustment. Consider total body weight and renal function. Duration of treatment is similar to that in other age groups [24].

UTI in Patients with Spinal Cord Injuries

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 [28]. Management focuses primarily on proper drainage of the bladder with intermittent catheterization reducing the risk of significant bacteriuria. Development of bacteriuria is all but certain with indwelling and suprapubic catheters. Presenting signs and symptoms have poor sensitivity and specificity, and, as such, caregivers should have a high index of suspicion. Identification of pyuria is generally considered the best indication of UTI in this group.

Fungal UTIs

Fungal UTI is most commonly caused by *Candida* and occasionally by *Cryptococcus neoformans*, *Aspergillus* species, and the endemic mycoses. Most fungal UTIs arise in the setting of urinary catheters, obstructed urinary tracts, diabetics, and those patients on antibiotic or immunosuppressive therapy.

For asymptomatic colonization with *Candida* (except following renal transplantation), no specific antifungal therapy is required. *Candida* cystitis is best treated with amphotericin B bladder instillation (50 μg/mL), systemic therapy (single-dose intravenous amphotericin B 0.3 mg/kg), or fluconazole 200 mg PO for 14 days.

Ascending pyelonephritis and *Candida* urosepsis require systemic antifungal therapy with IV amphotericin B at 0.6 mg/kg/day, duration depending on severity but in general involving a total dose of 2 g. An alternative is fluconazole at 5–10 mg/kg/day (IV or PO) [29].

Laboratory Guides and Interpretation

Pyuria

From a practical standpoint, pyuria represents readily measurable evidence of host injury. The most accurate method, or gold standard, of defining significant pyuria is the leukocyte excretion rate. There is evidence that the significant rate is 400,000 white blood cells (WBC)/h [30]. This measurement is cumbersome – hence the popularity of quicker, simpler, but less accurate screening tests. Those screening tests include microscopic

Table 1 Diagnostic information on common 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

examination of unspun urine in a counting chamber (WBC/mm^3), spun urine under a coverslip (WBC/hpf), and leukocyte esterase [31]. In general, the WBC/hpf is approximately 11 % of the WBC/cubic mm^3 [32]. 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 immediate, simple results with accuracy. The most common tests are direct microscopy and the dipstick (nitrite and leukocyte esterase). Commonly used screening tests with approximated diagnostic information are shown in Table 1.

Urine Culture

It is important to realize 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.

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 [28] and Eisenstadt and Washington [33]

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Fluid, Electrolyte, and Acid–Base Disorders

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Fluid, electrolyte, and acid–base disorders are frequently encountered in family medicine. Detecting and treating these disorders is imperative due to effects on organ perfusion [1]. These disorders present in all age-groups and various clinical settings; but those with chronic diseases are particularly vulnerable to serious complications [2, 3].

Volume Depletion

Volume depletion occurs with both actual volume loss and with relative volume loss by fluid redistribution (such 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. 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

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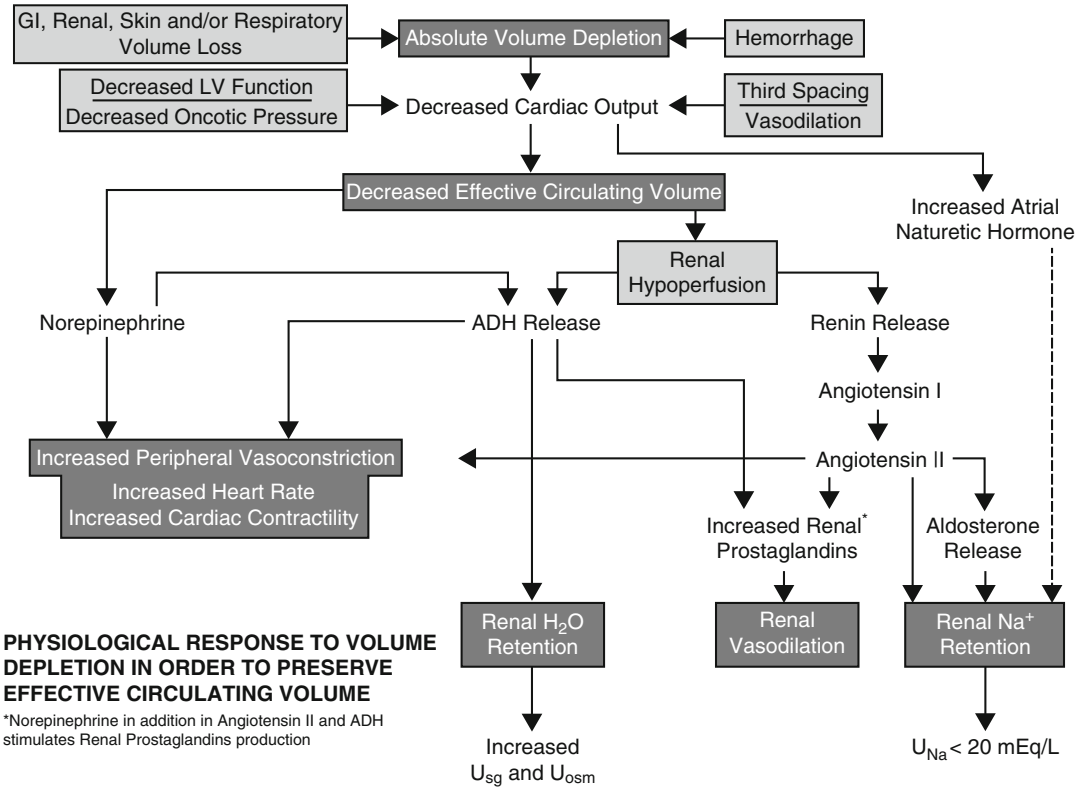

Fig. 1 Physiological response to volume depletion. *GI* gastrointestinal, *LV* left ventricle, U_{Na} urine sodium concentration, U_{osm} urine osmolality, U_{sg} urine specific gravity, *ADH* antidiuretic hormone, *SIADH* syndrome of inappropriate ADH secretion (Originally appeared in: Taylor R, David A, Fields S, Phillips M, Scherger J, editors. Family medicine (Taylor). New York: Springer; 2003)

antidiuretic hormone (ADH) release and activates the renin-angiotensin-aldosterone system (RAAS). 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 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. Use of nonsteroidal anti-inflammatory drugs (NSAIDs) and angiotensin-converting enzyme inhibitors (ACE-I) may diminish this renoprotective response [4–6].

Determining true volume status can be challenging even for an experienced physician. Accurate volume status can be especially difficult with the young, elderly, or disoriented patient. Clinically, volume depletion can manifest with low blood pressure, palpitations, dizziness, decreased urine output, and lightheadedness. Objective findings in volume depletion include resting tachycardia, orthostatic hypotension, resting hypotension, however some patients with hypovolemia may not exhibit abnormal vital signs. Chronic hypotension manifests more subtle findings such as general malaise, weakness, anorexia, and mental status changes. Volume status is also difficult when patients appear fluid overloaded (e.g., congestive heart failure [CHF], cirrhosis, and nephrosis) due to excessive renal sodium and water conservation that drives volume disproportionately to the interstitial fluid space

which is known as third spacing. Third spacing refers to the interstitial space between skin and fascia that is not normally perfused with fluids. Third spacing 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). Regardless of the cause, third spacing results in decreased intravascular volume. Physical exam findings can be varied due to differing etiologies, however edema is generally present.

Laboratory data can help determine fluid status such as serum osmolality (SOSM), blood urea nitrogen (BUN), urine osmolality (UOSM), and urine specific gravity. With volume depletion the urine specific gravity and UOSM are high (i.e., >1.015 and >350 mOsm/kg, respectively) as a result of ADH-induced renal water conservation leading to concentrated urine. In volume-depleted states, renal hypoperfusion results in prerenal azotemia and functional or nonintrinsic acute renal failure causing BUN to be retained such that the normal 10:1 BUN/creatinine ratio is elevated (e.g., to >20:1). When volume loss is due to hemorrhage, a hematocrit/hemoglobin can be low, however concentration 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.

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 postural blood pressure, pulse changes, and urinary excretion of sodium [5]. 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 edema may be found in the lower extremities in an ambulatory patient but may be more evident in the presacral area in a recumbent patient. Volume excess may present as pulmonary edema, elevated jugular venous pressure, or prolonged hepatojugular reflux in CHF. Additionally, volume excess may not be readily evident on clinical exam as in a patient with bowel wall edema [7]. 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 caused by decreased ECV involves increasing cardiac output in heart failure patients and restoring intravascular oncotic forces in patients with cirrhosis and hypoalbuminemia. Removal of some edema by diuretics may be required, typically in the form of intravenous furosemide, 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 reaccumulations extracted from the circulating volume, resulting in hypotension. 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. Careful and deliberate diuresis is very important in CHF.

Sodium Disorders

Appreciating a patient's fluid status is crucial when disorders of sodium concentration are present. Hyponatremia ($[Na^+]$ <135 mEq/L) and hypernatremia ($[Na^+]$ >145 mEq/L) should be approached in terms of free water level status. A firm understanding of tonicity is required when approaching sodium disorders.

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 the membrane (cellular membrane) while osmolality is the property of a particular solution. These compartmentalized solutes create an osmotic gradient across the cell membrane [8]. In effective plasma osmolality, which is typically normal within the range of 275–300 mOsm/kg H_2O, only solutes that predominantly do not pass between the ECF and ICF contribute to creating osmotic gradients and effecting flow of water between the ECF and ICF. Sodium is a major plasma solute, and therefore when evaluating hyponatremia, the osmolality should be evaluated.

The plasma osmolality (POSM) is the total osmolality of the solutes in the plasma and can be calculated as

$$P_{\text{osm}} = 2[\text{Na}^+] + \frac{[\text{glucose}]}{18} + \frac{[\text{BUN}]}{2.8}$$

Calculating the effective POSM can be helpful and when different from measured (osmolality gap) can indicate the presence of ethanol, methanol, isopropanol, ethylene glycol, propylene glycone, or acetone. Therefore, evaluating plasma osmolality, effective and measured, would be the first step when approaching sodium disorders. Determining osmolality is also needed when approaching metabolic acidosis disorders which will be discussed later.

Hyponatremia

Hyponatremia (Table 2) and hypoosmolality (i.e., plasma osmolality <275 mOsm/kg) indicate excess water content relative to sodium caused by renal retention of ingested water such as hypovolemic-induced ADH release, SIADH, and excess water ingestion greater than renal free water clearance. Hyponatremia occurs without hypoosmolality (i.e., pseudohyponatremia) in the presence of hyperproteinemia and hyperlipidemia. Pseudohyponatremia can occur with severe hyperlipidemia (hypercholesterolemia and hypertriglyceridemia) and hyperproteinemia (such as multiple myeloma), causing relatively lower proportions of sodium in plasma but maintaining normal osmolality and tonicity between 275 and 300 mOsm/kg H_2O [9–11].

Hyperglycemia is discussed more completely in chapter "▶ Diabetes Mellitus"; however, it is also important to consider its impact on fluid and electrolyte abnormalities. In states where serum glucose is highly elevated, fluid shifts can be profound and electrolyte imbalance substantial. Excessive hyperglycemia obligates large amounts of additional water to extracellular spaces by osmotic-induced intracellular water loss (i.e., cellular dehydration). When evaluating hyperglycemia, the correct sodium should be calculated.

Corrected sodium = Measured sodium + 0.024 × (serum glucose – 100) [12]

Hyperglycemia causes an osmotic diuresis leading both to salt and water losses, total body volume depletion, or decreased renal perfusion. As kidney perfusion decreases, renal ability to excrete glucose is impaired further contributing to hyperglycemia. The hyperglycemic diuresis contributes to total body potassium losses through

urine, though overt hypokalemia may not be evident until fluid loss is replaced and insulin given. Potassium deficits can inhibit cellular glucose uptake and cause cardiac dysrhythmias.

Volume repletion is paramount in treating hyperglycemic episodes and leads to decrease in serum glucose and improved glomerular filtration rate. Isotonic saline is initially preferred, attending to possible hemodynamic instability, and should be started at 15–20 mL/kg/h decreasing to 4–14 mL/kg/h once patient has stabilized [13]. In hyperosmolar hyperglycemic nonketotic syndrome, insulin is a required therapy, though it should not be given until fluid resuscitation is initiated since insulin drives glucose, potassium, and water into cells potentially causing vascular collapse. In diabetic ketoacidosis, higher doses of insulin via continuous infusion are usually required. In order to avoid cerebral edema, fluid should be switched to 0.45 % normal saline when sodium is greater than 135 mmol/L with 5 % dextrose added once plasma glucose is 200 mmol/L [14].

Hypernatremia (see Fig. 3) and hyperosmolality (i.e., plasma osmolality >300 mOsm/kg) reflect a water deficit relative to sodium caused by excess water loss, decreased water intake, decreased water retention, or excess intake of sodium salts.

Understanding osmolality and tonicity is crucial to understanding hyponatremia (Fig. 2), which is the most common occurring electrolyte abnormality [15]. Clinically, hyponatremia can be further categorized by determining volume status [16]; there are three types of hyponatremia: hypovolemic, euvolemic, and hypervolemic. Common causes for hyponatremia are shown in Table 1.

Low-volume 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 with water retention [8]. UNa concentration can be a helpful measure of these mechanisms as UNa >20 mmol/L represents sodium loss mediated by the kidneys [17]. In hypovolemic hyponatremia, ingested free

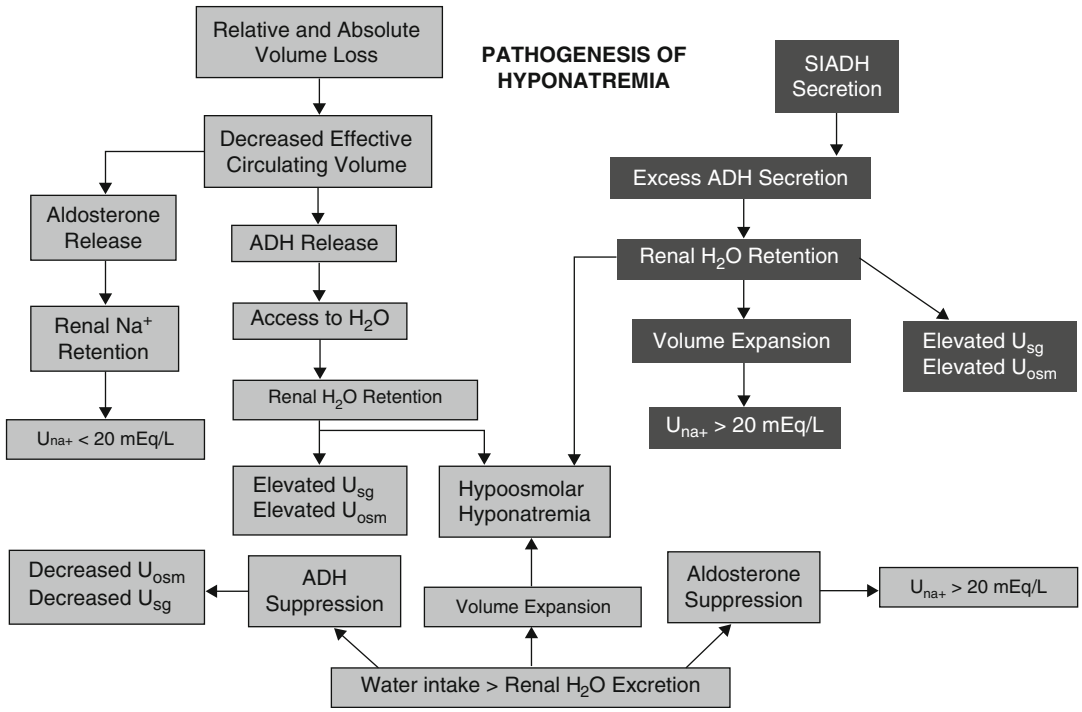

Fig. 2 Pathogenesis of hyponatremia. U_{Na} urine sodium concentration, U_{osm} urine osmolality, U_{sg} urine specific gravity, *ADH* antidiuretic hormone, *SIADH* syndrome of inappropriate ADH secretion (Originally appeared in: Taylor R, David A, Fields S, Phillips M, Scherger J, editors. Family medicine (Taylor). New York: Springer; 2003)

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 potomonia	Acute or chroni renal failure
Sweat losses	Dilute formula intake	
Third-space sequestration	Dilute tube-feeding	

References used: [1, 17, 36]
ADH antidiuretic hormone, *GI* gastrointestinal, *SIADH* syndrome of inappropriate secretion of ADH, *ECV* effective circulating volume, UNa urine sodium concentration

water is retained because of the nonosmotic (i.e., hypovolemia-induced vasoconstriction) presence of ADH acting in the distal convoluted tubule and collecting duct [18–21]. With hypovolemic hyponatremia from diuretic use, most commonly thiazide diuretics, the dilutional mechanism in the tubules is inhibited, but UNa concentration is not [21–25]. Thiazide-induced hyponatremia is more common in elderly women than men [26, 27]. Mineralocorticoid deficiency from adrenal gland destruction or inherited deficiencies 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 is another cause of hypovolemic hyponatremia. 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. Chronic use of proton pump inhibitor-induced hyponatremia is increasingly being elucidated in literature and adds further concerns to long-term proton-pump inhibitors (PPI) use [28]. The PPI-mediated hyponatremia mechanism is unclear but likely related to SIADH or sodium-losing nephropathy [29]. Extrarenal losses leading to hypovolemic hyponatremia include GI losses (i.e., vomiting and diarrhea) and third-space sequestration (i.e., bowel obstruction, pancreatitis, peritonitis, ascites, massive tissue injury, venous congestion). Urine sodium concentrations in these causes are usually <20 mEq/L.

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) [15, 30]. SIADH is the most common form of euvolemic hyponatremia and occurs when excess ADH is secreted in the absence of volume or osmotic stimuli, resulting in water excess and hyponatremia caused by a variety of disorders including central nervous system and pulmonary diseases (Table 2). Euvolemic hyponatremia can occur in exercise-associated hyponatremia. Interestingly, long-distance running athletes who consumed excessive amounts of water during competition in conjunction with ADH-stimulatory effects of exercise intensity and duration led to hyponatremia [35]. Primary polydipsia [30] (i.e., ingestion of large quantities of water 10–15 L in 24 h) leads to hyponatremia since intake exceeds the kidneys' ability to excrete free water.

Diseases that increase ECF volume through elevated ADH and frequently reduced glomulelar filtration rate (GFR) (e.g., CHF, cirrhosis, nephrotic syndrome, severe renal insufficiency) can lead to hypervolemic hyponatremia [36, 37].

Table 2 Causes of syndrome of inappropriate antidiuretic hormone secretion

Central nervous system disorders causing increased hypothalamic production of antidiuretic hormone
Infections (e.g., meningitis, HIV infection)
Vascular problems (e.g., subdural hemorrhage)
Primary and metastatic cancers
Psychosis
Post pituitary surgery
Hypothalamic infiltrative disease (e.g., sarcoidosis)
Others (e.g., Guillain-Barré syndrome)
Pharmacologic agents
Stimulants of hypothalamic antidiuretic hormone secretion- Haloperidol, Amitriptyline, Thioridazine, Thiothixene, Carbamazepine, Fluoxetine and sertraline, Monoamine oxidase inhibitors, and others
Potentiators of antidiuretic hormone effect- Chlorpropamide, Tolbutamide, Carbamazepine
Exogenous antidiuretic hormone preparations- Vasopressin, Oxytocin
Pulmonary disorders causing increased antidiuretic hormone production
Pneumonias
Tuberculosis
Acute respiratory failure
Others (e.g., asthma, pneumothorax)
Ectopic production of antidiuretic hormone (e.g., bronchogenic carcinoma, oat cell carcinoma of the lung, pancreatic carcinoma)
Pancreatic carcinoma
Prolactinoma
Others
Postoperative patient
Severe nausea

Adapted from: [1, 31–34]

ADH secretion increases in left heart function and decreases due to baroreceptor mechanisms. [37] Low levels of circulating protein in both cirrhosis and nephrotic syndrome lead to hyponatremia through an ultimate decrease in intravascular volume, leading to release of ADH. Edematous causes of hyponatremia from aforementioned conditions are associated with weight gain and edema formation.

Hyponatremia-related symptoms vary depending on the cause of hyponatremia. Patients may be asymptomatic depending on the cause or present with confusion, weakness, irritability, nausea, vomiting, postural dizziness, syncope, and falls, with seizures and coma less common. [38] Symptoms are usually present when serum sodium approaches <120 mEq/L. In severe hyponatremia, neurological symptoms may include seizures and coma. The severity of symptoms depends not only on the level but the rapidity of decline. Patients who develop hyponatremia over time may remain asymptomatic at relatively lower levels of plasma sodium concentration because of brain cell adaptation to hypoosmolality [39].

Treatment of hyponatremia is dependent on the expected cause. In hypoosmolar hyponatremia from volume loss, sodium replacement should almost always be with oral or intravenous isotonic volume repletion. In patients with neurological symptoms or plasma sodium <110 mEq/L infusion of hypertonic saline with free water fluid restriction are often both 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. For patients with hyponatremia caused by SIADH and those with severe renal failure, re-equilibrating plasma osmolality is done via fluid restriction. Identifying and removing the source of SIADH secretion is also key. Plasma sodium concentration correction for asymptomatic patients with SIADH should be increased at a rate of 0.5 mEq/L/h until a level of 120 mEq/L is reached; however, more rapid sodium correction might be necessary for those patients with severe neurological symptoms (1.0–1.5 mEq/L/h for the first 10 mEq/L elevation in the plasma sodium concentration). Avoiding excessively rapid correction of hyponatremia decreases the possibility of potentially devastating central pontine demyelinization [40–49]. With hypervolemic hyponatremia, focus of therapy is on restoring ECV by improving ventricular dysfunction in patients with CHF and increasing oncotic pressures in those with nephrosis and cirrhosis. Tolvaptan, a V_2 receptor antagonist, has been approved for treatment of euvolemic and hypervolemic hyponatremia for serum sodium <125 mEq/L or hyponatremia resistant to fluid restriction. This therapy must be done in

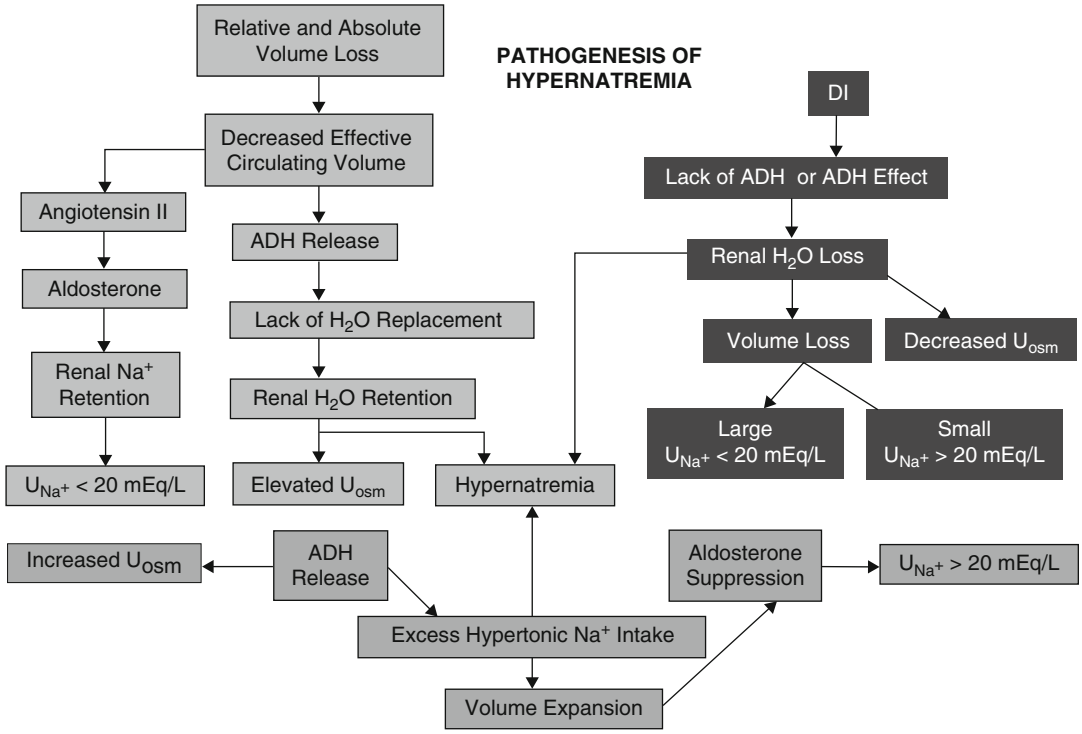

Fig. 3 Pathogenesis of hypernatremia. *DI* diabetes insipidus. (See Fig. 2 for other abbreviations.) (Originally appeared in: Taylor R, David A, Fields S, Phillips M, Scherger J, editors. Family medicine (Taylor). New York: Springer; 2003)

a hospital setting and fluid restriction not be initiated. Tolvaptan dosing remains controversial in preventing the overall disease progression in heart failure [50].

Hypernatremia

Hypernatremia, serum sodium concentration >145 mmol/L (Fig. 3), is caused by increased hypotonic fluid loss (i.e., GI losses, renal loss, insensible losses, or diabetes insipidus where ADH activity or secretion is reduced) exceeding hypotonic fluid intake [31–34, 51–53]. Approximately 1–3 % of all hospitalized patients are found to have hypernatremia [53, 54]. Thirst and access to water are the two most important aspects in preventing hypernatremia [55]. Excessive oral intake of sodium salts and hypertonic volume expansion can also lead to hypernatremia [56] (Table 3).

Table 3 Causes of hypernatremia

Primary Hypodipsia (defect of thirst)
Primary or metastatic tumor, granulomatous disease, vascular disease, trauma
Diabetes Inspidius
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

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) suggests diabetes insipidus, intrinsic renal disease, osmotic diuresis, or diuretic use [52, 53, 57].

The symptoms of hypernatremia occur due to hyperosmolality of ECF shifting volume out of cells. The rate and severity at which this process occurs dictates symptom development. The most dangerous symptoms are nonspecific weakness and agitation, which signal changes in central nervous system. As hypernatremia increases falls and syncope from disorientation and somnolence are more common. [58] Polyuria can 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. Also, hypertonic volume expansion or other addition of sodium salts can lead to a patient with the appearance of clinical volume overload (i.e., shortness of breath, pulmonary and peripheral edema, weight gain, systemic and venous hypertension, and S_3 gallop).

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 [59]. In cases when hypernatremia has developed in less than 48 h, or acute hypernatremia, correction can proceed at up to 1 mEq/L/h [59]. Hypernatremia correction that is too slow can also cause complications [60]. 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 [3, 60]. 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 × $(1–140/Na^+)$ [61]. Previously, treatment of central diabetes insipidus was with administration of ADH preparation (e.g., aqueous vasopressin, vasopressin in oil, and vasopressin nasal sprays); however, DDAVP (desmopressin) is preferred due to the side effect profile and variable efficacy of ADH preparations [62, 63]. Correcting other electrolyte abnormalities and removing the offending agent, which is frequently drug induced, treat nephrogenic diabetes insipidus. Thiazides and a low-sodium diet can be helpful in treatment as well.

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 is a common electrolyte abnormality and commonly the result of non-potassium sparing diuretics. As with hyponatremia (Table 4), plasma hypokalemia can occur due to nonrenal causes with urine potassium (UK) <25 mEq/L (e.g., excessive GI, skin potassium losses) and due to renal causes with UK >25 mEq/L (e.g., sodium-

Table 4 Causes of hypokalemia

Renal potassium loss
Diuretics, current use
Vomiting and nasogastric tube drainage
Magnesium depletion
Mineralocorticoid excess (e.g., primary and secondary hyperaldosteronism, Cushing's disease, licorice ingestion, hyperreninism, Bartter syndrome, Adrenal Adenoma)
Diabetic ketoacidosis
Renal tubular acidosis
Ureterosigmoidostomy
Polyuria
Osmotic diuresis
Correction of chronic hypercapnia
Gastrointestinal loss
Diarrhea
Excess sweating
Intestinal fistulas
Rectal villous adenoma
Geophagia (i.e., clay ingestion)
Laxative abuse
Chloride-losing diarrhea
Intracellular K^+ sequestration
Metabolic and respiratory alkalosis
Excess insulin
Treatment of megaloblastic anemias
Granulocyte-macrophage colony-stimulating factor (GM-CSF)
β-adrenergic agonist
Hypothermia
Catecholamine excess
Hypokalemic periodic paralysis
Pseudohypokalemia
Prolonged standing of collected blood with extremely high WBC count
Blood specimen collected immediately after insulin administration
Decreased K^+ intake
Starvation

Adapted from Taylor R, David A, Fields S, Phillips M, Scherger J, editors. Family medicine (Taylor). New York: Springer; 2003

losing nephropathies, mineralocorticoid excess, vomiting, diuretics, and hypomagnesemia). However, hypokalemia may be more easily categorized by potassium excreted via kidneys or potassium loss through GI tract or cellular shifts (i.e., potassium driven intracellularly).

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.

Potassium can be lost through the GI tract as well with diarrhea often associated with a hyperchloremic metabolic acidosis. Upper GI potassium loss from vomiting is mediated by hypovolemic-induced RAAS activation, along with high levels of sodium bicarbonate and increased distal flow to nephron where potassium is excreted. Also, vomiting causes chloride deficit that leads to metabolic alkalosis that may cause intracellular movement of potassium. The Na-K-ATPase pump in skeletal muscle and hepatocytes regulates most of the total body potassium and can be a source of hypokalemia with pump derangement (reference number here). Increased insulin activity drives potassium intracellularly by increasing pump activity, while β-adrenergic agonists are active at the Na-K-ATPase pump, as well as in the Na-K-2Cl (NKCC2) cotransporter [64, 65].

Metabolic and respiratory alkalosis, hypothermia, and hypokalemic periodic paralysis are also related to extracellular potassium moving intracellularly. As alkalotic states may drive potassium into cells, acidotic states like diabetic ketoacidosis and renal tubular acidosis (RTA) associated with increased UK loss and total body potassium depletion may cause an acidosis-induced increase in plasma potassium and corrected by treating acidotic state.

Hypokalemia coexisting with hypertension should be further evaluated by checking renal levels. If the renin levels are low, the aldosterone level should be measured to evaluate for primary hyperaldosteronism (i.e., high aldosterone levels) or exogenous mineralocorticoid (i.e., low

aldosterone levels as in licorice ingestion). High or normal renin levels can be associated with renovascular hypertension and Cushing's disease. Inadequate potassium intake alone can also cause hypokalemia [66]. Treatment of severe megaloblastic anemias or use of granulocyte-macrophage colony-stimulating factor induces cell production that leads to uptake of hypokalemia [67].

Hemolysis during collection of blood products can lead to spuriously elevated levels of plasma potassium, while also conveying normal plasma potassium when there is true hypokalemia.

Symptoms associated with hypokalemia include generalized weakness, musculoskeletal complaints (muscle cramps, muscle tenderness), GI complaints (anorexia, nausea, vomiting, 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 [68]. 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. Intravenous potassium chloride may be used solely or with oral therapy. Typically, 10 mEq of potassium supplementation will increase plasma potassium level by about 0.1 mEq/L with the potassium goal of 4.0 mEq/L to minimize untoward effects of hypokalemia. Foods rich in potassium are less useful in treatment of hypokalemia since potassium in these sources is in the form of potassium citrate or potassium phosphate, which is about 60 % less retained than potassium chloride [69]. Hypokalemia can be corrected intravenously via peripheral line at about 10 mEq/h since higher concentrations cause local irritation along with venous sclerosis. A central line can avoid these adverse effects when an infusion rate of 20 mEq/h or greater is required. In all cases of potassium repletion, frequent plasma potassium measurements should be monitored for efficacy of therapy [70]. Low magnesium must be corrected to ensure potassium is not lost renally during repletion [71]. Diuretics that work in the distal convoluted tubule and antagonize aldosterone receptors (i.e., spironolactone) can decrease kaluresis that is caused by loop and thiazide diuretics.

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 potassium. Extracellular potassium concentration can be affected by potassium shift from intracellular space to extracellular, potassium intake and potassium excretion [72]. The kidneys perform most potassium excretion. Many medications can lead to hyperkalemia. Spironolactone, ACE-I, ARBs decrease aldosterone production,

Table 5 Causes of hyperkalemia

Increased K^+ intake
Decreased K^+ excretion
Acute and chronic renal failure
Decreased effective circulating volume
Hypoaldosteronism- K^+-sparing diuretics, Hyporenin hypoaldosteronism in mild renal disease, NSAIDs, ACE inhibitors, Adrenal insufficiency
Intracellular K^+ extrusion
Metabolic and respiratory acidosis
Tissue injury (e.g., crush, rhabdomyolysis, hematoma resorption)
Insulin deficiency in diabetic ketoacidosis, prolonged fasting; hyperosmolality from hyperglycemia
Drugs (e.g., digitalis intoxication, succinylcholine, and arginine HCI, β-adrenergic blockers)
Hyperkalemic periodic paralysis (from excessive exercise, fasting)
Measurement error
Thrombocytosis
Leukocytosis
Hemolysis of blood sample (i.e., delay after blood draw, cell destruction from vigorous sample shaking
Blood collection from ischemic extremity

References used [1, 75–78]

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 [73]. Avoiding a combination of these medications in patients with coexistent renal failure is important [73]. Kidney dysfunction (RTA type 4, CHF, and other causes of hypoaldosteronism) can inhibit potassium excretion [72]. 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) [74] 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., $>1{,}000{,}000/mm^2$) [74–76].

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) [77]. 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 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 [78]. Sodium bicarbonate has not shown to be more effective than placebo [78]. Loop diuretics are effective for excreting total body potassium in patients who make urine and kayexalate. Sodium polystyrene was previously shown to be effective [72], but new data shows no difference compared to stool softeners alone and is associated with increased risk of intestinal necrosis [77, 79, 80]. In patients refractory to these treatments, hemodialysis may prove necessary [78].

Acid–Base Disorders

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 [81–84]. 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

Table 6 Causes of hypobicarbonatemia[a]

Metabolic acidosis (i.e., decreased pH, decreased[b] and decreased pCO_2[c])
Hyperchloremia, normal anion gap
Bicarbonate loss (hypokalemia and urine pH < 5.5)
GI tract bicarbonate loss (e.g., diarrhea, ureterosigmoidostomy, fistulas, tube drainage)
Renal bicarbonate loss and production failure (e.g., RTA Type 2, RTA Type 1, RTA Type 4, carbonic anhydrase inhibitors)
HCl addition (e.g., NH_3Cl and some hyperalimentation fluids)
Hypoaldosteronism (hyperkalemia, submaximal urinary acidification)
Primary adrenal insufficiency
Hyporeninemic hypoaldosteronism (e.g., during early chronic renal failure, acute renal failure interstitial nephritis, angiotensin-converting enzyme inhibition, and nonsteroidal antiinflammatory drug use)
Aldosterone resistance (e.g., spironolactone, amiloride, triamterene)
Intestinal nephritis
Early renal failure
Acute renal failure
Initial recovery from organic acidosis (variable $[K^+]$ and urine pH)
Normochloremia, large anion gap (urine pH < 5.5)
Excessive production of endogenously generated organic acids
Diabetic ketoacidosis (i.e., excessive β-hydroxybutyrate and acetoacetate)
Starvation ketosis
Alcoholic ketosis
Lactic acidosis
Muscle necrosis
Decreased excretion of endogenous acid metabolites
Renal failure
Ingestion of exogenous agents causing organic acidosis
Methanol
Ethylene glycol
Paraldehyde
Salicylates
Respiratory alkalosis (i.e., increased pH, decreased $[HCO_3^-]$[c] and decreased pCO_2[b])
Increased CNS stimulation
Physiologic and psychogenic hyperventilation
CNS disease (e.g., infectious, trauma, infarct, bleeding, tumors, heat stroke)
Pregnancy
Progesterone-producing tumors
Hepatic encephalopathy
Methylxanthines, nicotine, salicylates
Sepsis
Hypoxia
High altitude
Anemia, severe
Pulmonary embolus, pulmonary edema, pneumothorax
Carbon monoxide poisoning
Mechanical overventilation

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[a]Hypobicarbonatemia = decreased $[HCO_3^-]$

[b]Primary acid–base event

[c]Secondary or compensatory acid–base event

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) [85], 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 [86–88]. 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;

$$\text{Anion Gap} = [\text{Sodium}] - [\text{Chloride}] - [\text{HCO3}]$$

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).

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) [74]. 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 [89].

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 overactivity, peripheral arteriolar vasodilation, hyperkalemia, and cerebral vasodilation with resultant increased intracranial pressure. Many of these conditions can be deleterious and deadly. Therapy 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. Severe forms of metabolic acidosis therefore require administration of sodium bicarbonate in amounts necessary to restore the pH to this safe level, with care taken to avoid volume excess and post-treatment metabolic alkalosis by overaggressive alkali therapy [90]. If the metabolic acidosis is severe enough to warrant alkali therapy, physician comfortable with use should manage it [89, 90].

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 [1]. 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 respiration may predominate as the mechanism of pCO_2 removal. Treatment is directed to the underlying cause.

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) [1]. 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 [1]. 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:

Table 7 Causes of hyperbicarbonatemia[a]

Metabolic alkalosis (i.e., increased $[HCO_3^-]$[b] increased pCO_2, increased pH)
Hypovolemia and chloride depletion (i.e., hypochloremia, hypokalemia: urine $Na^+ < 10$ mEq/L, $Cl^- < 10$ mEq/L, pH < 6, $K^+ < 10$ mEq/L
Vomiting
Postdiuretic use
Congenital chloride diarrhea
Bartter syndrome
Acute correction of hypercapnia in hypovolemia
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
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 (e.g., $NaHCO_3$)
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
Drugs (e.g., sedatives
Oxygen-induced acute pCO_2 retention in chronic obstructive pulmonary disease (COPD)
Sleep apnea
Disorders of respiratory muscles
Obstructed airway
Extrinsic foreign body
Aspiration
Laryngeal edema or spasm
Bronchospasm
Disturbances of gas exchange across alveolar membrane
Pulmonary edema
Adult respiratory distress syndrome
Diffuse pneumonia
COPD
Loss of ventilatory volume
Pneumothorax
Hemothorax
Pleural effusions

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[a]Hyperbicarbonatemia = increased $[HCO_3^-]$

[b]Primary acid–base event

(1) excess CO_2 in the inhaled gas, (2) decreased alveolar ventilation, (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 hypercapnia. The treatment of respiratory acidosis is directed to the primary cause to increase the effectiveness of ventilation and pulmonary gas exchange.

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

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

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 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).

Misc. 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 [1]. 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 intracellular magnesium redistribution (e.g., diabetic ketoacidosis and alcoholism).

Hypermagnesemia (Mg^{2+} > 2.5 mEq/L) results when magnesium intake exceeds renal excretion (UMg > 20 mg/day) and when there is decreased renal excretion (UMg < 20 mg/day) caused by excessive renal magnesium tubular reabsorption (e.g., hyperparathyroidism, hypovolemia, hypocalcemia, and hypothyroidism) and GFR (e.g., acute and chronic renal failure and hypovolemia).

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 [1]. 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 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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1 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.

1.1 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, 4, 12]. 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, 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].

1.2 Immunoglobulin A Nephropathy

IgA nephropathy is perhaps 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 Renal Disease (ESRD). IgA nephropathy often accompanies Henlock-Shonlein 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 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 [2].

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1.3 Lupus Nephritis

Patients with systemic lupus erythematosis 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 although as a second-line agent [3].

1.4 Rapidly Progressive Glomerulonephritis

RPGN, also known as crescent glomerulonephritis, is a dramatic condition causing a rapid, often irreversible, decline in renal function. In fact, if left untreated it uniformly leads to ESRD or death. Crescents are cellular elements that follow the contour of Bowman's capsule, crowding out the capillary loops in the glomerulus, thus the term crescentic glomerulonephritis. 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.

1.4.1 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. As there often is a delay in receiving the results of Anti-GBM antibody titers a kidney biopsy is often necessary in order to establish the diagnosis. Intravenous steroids, cyclophosphamide, and plasmapheresis if used early in the course of the disease are usually effective in improving renal function and controlling pulmonary hemorrhage. As this is an antibody mediated disorder, the 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 [4].

1.4.2 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. What sets this disorder apart is the presence of crescents which are just 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 ESRD. Most of these glomerular diseases are idiopathic, however. Therapy consists of intravenous steroids and cytotoxic drugs with less reliance on plasmapheresis. Again, early initiation of therapy is critical if ESRD is to be avoided.

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1.4.3 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. Despite the lack of demonstrated immune complexes deposited in the glomerulus, 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) or granulomatosis with polyangiitis (GPA) (Wegner granulomatosis) and eosinophic granulomatosis with polyangiitis (EGPA). These disorders are systemic diseases and many organ systems are often affected simultaneously. Flu-like symptoms often occur for weeks in these individuals. Rash usually purpuric, arthralgias, symptoms of a peripheral neuropathy, and nonspecific pulmonary symptoms including pulmonary hemorrhage and chronic sinusitis may be present. Asthma is the prominent symptom in most patients but any organ can be involved by this small and medium sized vessel vasculitis. 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. >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 antigen targets (positive c- and p-ANCA). As with the other types of RPGN, early diagnosis and therapy is essential in order to avoid ESRD. Dramatic response to intravenous steroids and cyclophosphamide is the rule with a >90 % response rate. 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 despite remission so close, regular follow-up is essential [5].

2 Nephrotic Syndrome

Nephrotic syndrome is characterized by heavy proteinuria in association with hypoalbuminemia, edema, and hyperlipidemia. In contrast to nephritic sediment, cellular casts and hematuria are uncommonly encountered in nephrotic syndrome.

2.1 Clinical and Laboratory Features

The typical presenting symptom of nephrotic syndrome is progressive edema. Edema generally starts in the lower extremities; however, 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. More recently, studies have suggested that there is 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) [6]. 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. Moreover, not all patients with nephrotic range proteinuria have nephrotic syndrome, which is accompanied by edema, hypoalbuminemia, and hyperlipidemia. 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 semi-quantitative

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screening tool available to most physician providers. In addition, the spot urine protein to creatinine ratio is easy to use in the clinic setting, and provides a quantitative value that accurately 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 from 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 have increased risk of venous thromboembolism. Moreover, patients with membranous nephropathy as well as those with severe disease, with albumin levels less than 2 mg/dL or proteinuria greater than 10 g in 24 h, appear to be at 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 [7]. 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 [8]. 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.

2.2 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 effect 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 (Table 2). 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

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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Table 2 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 (cyroglobulinemia, 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)

of enlarged kidney sizes in diabetes and infiltrative disease states. A kidney biopsy is often indicated to help 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 a high clinical suspicion for diabetic nephropathy.

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2.3 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; and 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.

2.4 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 ESRD 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 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.

2.5 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 literature has found an association between idiopathic membranous nephropathy with antibodies against phospholipase A2 receptors found on podocytes [9]. 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 men, 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 [10]. 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 [11, 12].

2.6 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.

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2.6.1 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 that can be implemented for the nephrotic syndrome, irregardless 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. Angiotensin-converting enzyme inhibitors (ACE Inhibitors) or angiotensin receptor blockers (ARBs) in addition to their antihypertensive effects reduce intraglomerular pressure; this in turn can reduce proteinuria [13]. 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 as well.

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.

3 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 proteinturia, 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 [14].

3.1 Autosomal Dominant Polycystic Kidney Disease (ADPKD)

ADPKD is the most common inherited kidney disease and accounts for 10 % of the ESRD 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, 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 ESRD 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

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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

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 in these cysts. Infections in any cyst may be difficult to treat as antibiotic penetration into the cyst fluid may be variable. Antibiotics that penetrate the cyst wall are needed such as trimethoprim-sulfamethoxazole, quinolones, erythromycin, tetracyclines, or metronidazole. Cyst drainage may be necessary to successfully eradicate the infection. The most devastating complication of AKPKD is rupture of an intracerebral aneurysm. Up to 4 % of patients with ADPKD will have this complication. There seems to be a family predilection for this complication. 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 antagonisits (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 [15].

3.2 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,

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Table 4 Stages of AKI

	Assessment	
Stage	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

nephrogenic diabetes insipidus, or Fanconi syndrome may be the predominate manifestation. Non-nephrotic range proteinuria with minimal albuminuria often is seen. 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.

4 Acute Kidney Injury

Acute Kidney Injury (AKI) could be defined as the abrupt (within 1–7 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 about half of the patients admitted to ICU [16]. Importantly, community based cases comprise one third of all AKI cases [17]. AKI might be difficult to recognize, it does not have any specific symptoms. Detection might be particularly difficult in edematous patients with fluid overload dilution as they can have falsely lower serum creatinine (SCr). AKI typically develops in the setting of another illness and is associated with high mortality, especially in patients requiring dialysis. Term AKI replaced Acute Renal Failure to allow for an earlier detection and treatment of the AKI. 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. AKI is staged based on the severity of the impairment (Table 4).

The causes of AKI could be 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). It is important to determine the cause whenever possible , however most of the AKI cases in the hospital are multifactorial in etiology.

Prerenal AKI accounts for 70 % of the AKI in the outpatient setting [18] and for 21 % in the hospital [19]. Common causes include poor perfusion of the kidney due to hypovolemia, which could be caused by GI losses. 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, further promoting prerenal AKI by impairing renal auto regulation in the setting of hypovolemia. Patients with CKD are especially susceptible to developing AKI [20]. Fractional Excretion of Sodium (FeNa) is often used to differentiate between prerenal and renal causes of the AKI. It could be calculated using formula:

$$\mathrm{FE_Na} = \frac{100 \times \text{Urinary sodium} \times \text{serum creatinine}}{\text{Serum sodium} \times \text{urinary creatinine}}$$

FeNa <1 % is usually consistent with a prerenal cause of AKI. FeNa should be interpreted carefully: it might be low in AKI patients with contrast nephropathy, rhabdomyolysis, and urinary tract obstruction [21] while diuretic use could be associated with FeNa >1 %. A blood urea nitrogen to creatinine ratio >20 is often used to differentiate between prerenal and renal AKI. Recent data, however, does not support its use as a marker for prerenal AKI [22]. Prerenal AKI is often reversible, but can lead to ischemic AKI if not timely addressed.

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4.1 Intrinsic Renal AKI

Intrinsic renal causes could be further subdivided into tubular, glomerular, interstitial, or vascular causes 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, usually reversible but may require renal replacement therapy. Rapidly progressive glomerulonephritis can present as AKI. In the presence of active urinary sediment showing proteinuria, hematuria or casts 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. Acute Interstitial nephritis 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 of the patients. Clinical symptoms may include maculopapular rash, fever, and arthralgias. Corticosteroids have a role in the treatment of acute interstitial nephritis. Vascular causes of AKI comprise occlusion of the renal artery or disease of the abdominal aorta. Microvascular disease includes 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 plasmopheresis. Atheroembolic disease as a cause for AKI should be suspected in a patient with recent arterial intervention or after vascular surgery.

4.2 Contrast Induced AKI (CI-AKI)

This is one of the most common AKI found in the hospital setting. It typically occurs within 72 h of exposure to iodinated contrast and resolves over the following 5 days. Patients with normal kidney function have minimal risk for CI-AKI. Patients with an estimated GFR < 60 mls/min/1.73 m^2, sepsis, hypovolemia, over 75 years of age, intraabdominal pathology, and receiving nephrotoxic medications including NSAIDS are at increased risk. Estimated GFR could be used for assessment of kidney function in patients with CKD, SCr should be used for those with AKI. 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 0.9 % sodium chloride or isotonic sodium bicarbonate is recommended in patients identified as at high risk of CI-AKI [23]. 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 (22). *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 [24].

Postrenal AKI accounts for up to 10 % of the hospital and 17 % of the community AKI cases respectively and results from obstruction of urine flow at different levels. Both urinary tracts need to be obstructed for the AKI to develop unless the patient has single functioning kidney. Obstruction could be mechanical (prostate hypertrophy, prostate and cervical cancer, retroperitoneal fibrosis) or functional (neurogenic bladder). Relieving of obstruction is the treatment and should be done promptly to improve the chance of recovery.

4.2.1 AKI Risk Factors

A number of chronic diseases including diabetes mellitus and cardiovascular disease are associated with development of AKI. CKD and proteinuria [25] 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 [26] (Table 5), blood product transfusion, and underlying chronic heart, lung, and liver disease [27].

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Table 5 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

4.2.2 Diagnostic Evaluation

Careful interpretation of the clinical history, physical 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 findings of schistocytes may support the diagnosis of microangiopathic hemolysis. Finding monoclonal proteins in serum and/or urine might provide diagnostic clues. In some cases, when clinical history, diagnosis and imaging tests are not sufficient renal biopsy might be needed to make 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 of postrenal causes. Research continues to focus on identifying biomarkers of earlier kidney damage detectible before a change in SCr occurs, similar to cardiac biomarkers used for the evaluation of chest pain.

4.2.3 Prevention and Treatment of the AKI

Prevention of the AKI relies on the recognition of its potential causes, avoidance of possible renal insults whenever possible, and treatment of likely AKI triggers. 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 is mainly supportive and includes monitoring of volume status, SCr, and urine output and treatment of the 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) are often given followed by 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 [28] with close monitoring of serum electrolytes. 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

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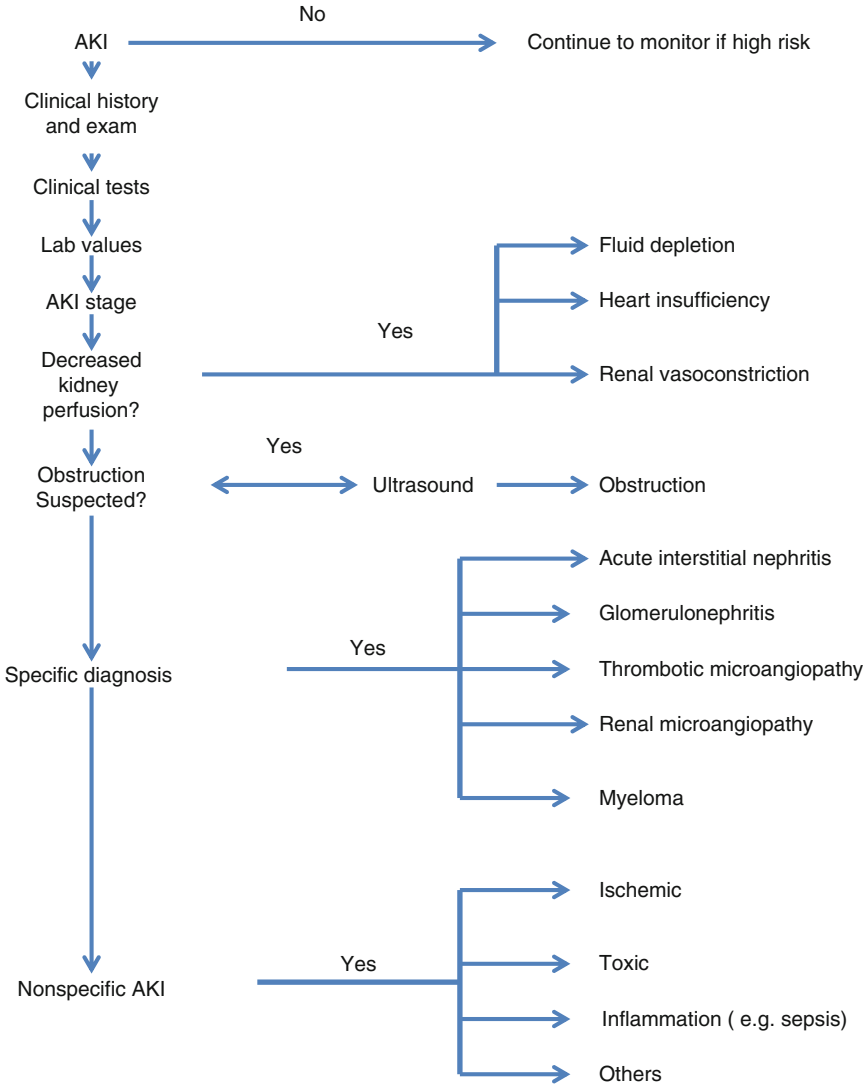

Fig. 1 Evaluation of AKI

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 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. Nutrition 20–30 kcal/kg/day in patients with any stage of AKI is recommended [23], enteral nutrition is preferred. After nephrology consult is obtained, consideration might be given to renal biopsy and disease specific treatment (steroids, plasmapheresis, immunosuppressive therapy) is initiated. For those who do not improve with conservative management or exhibit uremic complications like difficult to control hyperkalemia, metabolic acidosis or volume overload, renal replacement therapy might be required.

4.2.4 Follow Up Care

AKI is an important risk factor for CKD even among patients who recovered completely from this condition. Severity and number of the AKI episodes are risks for development of CKD [29]. Patients with history of AKI should be reevaluated in 3 months for AKI resolution, new onset, or worsening of the CKD [23].

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Table 6 Prognosis of CKD by GFR 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

5 CKD

CKD is a worldwide problem and is associated with increased mortality, morbidity, and health care costs. Disease affects an estimated 10 % or over 20 million adults in the United States and it is the eighth leading cause of death. one out of three patients with diabetes and one out of five patients with hypertension has CKD [30]. Patients with CKD are at significantly increased risks of cardiovascular disease and stroke [31, 32]. 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. About 1 % of CKD patients are treated with dialysis and/or kidney transplantation, primary care physicians manage most of the nondialysis CKD patients.

5.1 CKD Definition and Detection

CKD is defined by the presence of structural or functional abnormalities of the kidney with or without an accompanying reduction in Glomerular Filtration Rate (GFR). Patients with CKD may have one or more of the following: pathologic abnormalities, markers of kidney damage (i.e., imaging abnormalities and abnormalities in serum or urine, including proteinuria and abnormal urinary sediment), or GFR less than 60 mL per minute per 1.73 m^2 for at least 3 months. CKD is classified into five stages on the basis of GFR. Normal GFR in young adults is about 125 mL/min per 1.73 m^2; GFR < 15 mL/min per 1.73 m^2 is defined as kidney failure. Presence of albuminuria even with normal GFR signifies CKD. Recognition that patients with GFR < 45 ml/min per 1.73 m^2 experience faster disease progression [33] and that proteinuria affects CKD evolution and influences mortality led to modification of the guidelines in 2012 [34]. Table 6 outlines prognosis of CKD by GFR and albuminuria categories [34].

It is now recognized that CKD and AKI are closely connected: AKI can lead to CKD, if the duration of the abnormality is unknown, the possibility of AKI should be considered and appropriate evaluation performed for 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 [35]. 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 making screening important. When symptoms are present, they include fatigue, hypertension, edema, shortness of breath, leg cramps, poor appetite, and abnormal urination pattern. Two simple tests could identify CKD: serum creatinine to calculate the GFR and urinary albumin to creatinine ratio to detect albuminuria. Annual CKD screening for patients at risk is recommended by several professional organizations [36, 37]. The evidence to support CKD screening in asymptomatic adults is lacking.

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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)

5.2 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 usually presents as slowly progressing albuminuria, sometimes to the nephrotic range when albumin to creatinine ratio is usually over 2,200 mg per g or protein to creatinine ration is over 3,000 mg per g, hypertension and GFR decline. Hypertensive kidney disease might be associated with albuminuria that develops after GFR decline. Urinalysis can provide diagnostic clues to detection of glomerulonephritis, tubulointerstitial disease, vasculitis, hereditary nephritis, and lupus nephritis; however, it is not routinely recommended in otherwise healthy patients.

A thorough investigation is important in assessing CKD and includes determining the etiology and type of CKD whenever possible and evaluating for comorbidities. Proteinuria refers to increased excretion of any urinary protein, including albumin and other serum proteins (tubular proteins). A normal urinary protein-to-creatinine ratio is less than 200 mg per g; proteinuria is a 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. It is further subdivided into microalbuminuria, defined as albumin-to-creatinine ratio of 30–300 mg per g and macroalbuminuria when ratio exceeds 300 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 GFR should be assessed annually for patients with CKD [34] and small variations in GFR 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 the CKD diagnosis patients should be assessed to identify risk factors for progression: cause of CKD, level of GFR and albuminuria (lower GFR levels and higher degree of proteinuria are associated with CKD progression), age, race/ethnicity, elevated blood pressure, hyperglycemia, dyslipidemia, smoking, and exposure to nephrotoxic drugs.

5.3 Treatment

The goals of CKD treatment is to slow progression of CKD, reduce compilations of decreased GFR, 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 [37], assessment of cardiovascular risk factor 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 should be around 7 %. Level should be set at above 7 % for those with comorbidities, reduced life expectancy, and at risk for hypoglycemia

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[34]. Metformin may be continued in people with GFR $\geq$ 45 ml/min/1.73 m^2. Its use should be reviewed in patients with GFR 30–44 45 ml/min/1.73 m^2 and it should be stopped when GFR is 30 ml/min/1.73 m^2 or less [34].

Therapeutic strategies that have been shown to prevent cardiovascular events in patients with CKD include BP control, statins, and 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 [38]. Use of ACE inhibitors and ARBs is associated with delaying CKD progression including patients with advanced disease stages and, importantly, offers greater survival. They could be stopped temporarily in the setting of AKI and restarted when creatinine stabilizes. In patients with cardiovascular disease and CKD, levels of BNP and troponin should be evaluated carefully. Patients with an estimated GFR of less than 60 mL per minute per 1.73 m^2 require further evaluation to assess for 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. Decreased GFR affects pharmacokinetics and pharmacodynamics of many medications, increasing the risk of toxic effects if the dose is not appropriately adjusted. The multispecialty team should manage patients with advanced stages of CKD. Renal replacement therapy might need to be initiated to manage symptoms of kidney failure (serositis), acid-based and electrolyte abnormalities, control volume status, and blood pressure which occur when GFR falls below 10 ml/min/1.73 m^2. Preemptive renal transplantation should be considered for patients with GFR 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.

6 Renal Cell Carcinoma

Renal-cell carcinomas originate from the renal epithelium and account for about 90 % of renal cancers. Established risk factors include hypertension, obesity, and active and passive smoking [39]. Acquired renal cystic disease, ESRD, duration of dialysis and tuberous sclerosis are associated with increased risk for renal cell carcinoma as well. 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), autosomal dominant cancer disorder, 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) [40]. Patients with this syndrome develop multifocal and often bilateral renal tumors earlier in life; they require monitoring of the lesions size. Over 50 % of the tumors are found on the unrelated imaging studies [41] and about 10 % of the patients present with classic triad of symptoms: flank pain, palpable abdominal mass and hematuria. Patients might also present with nonspecific symptoms like fatigue, weight loss, anemia, and micro or gross hematuria. Hematuria should 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 [42]. Paraneoplastic syndromes include polycythemia from abnormal erythropoietin production, unexplained fever, hypercalcemia, and Stauffer syndrome: abnormal liver enzyme consistent with cholestasis jaundice and organomegaly in the absence of liver metastasis. Surgical excision (partial

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or total nephrectomy) is the main treatment for renal cell carcinoma. 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.

7 Transitional Cell Carcinoma

Renal transitional cell carcinoma accounts for only 7 % of all kidney tumors, but 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. 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. 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 [43]. The role of radiation treatment is not well stated, but might be beneficial to patients with stages T3/T4 cancer [43].

8 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 [44]. Over 90 % of the bladder cancer is transitional cell carcinomas. Nearly half of the patents are diagnosed when cancer is in earlier stages, ∼35 % have disease confined to the bladder and 4 % present with distant metastasis [44]. The incidence of bladder cancer increases with age peaking between 50 and 70 years. 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 as well. Evaluation includes urine cytology, cystoscopy, and imaging studies [45]. 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 [46]. 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 [45]. 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.

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9 Wilms' Tumor

Wilms' tumor 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 excessive renal secretion. 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 the number of factors including tumor size, stage of the disease, the diagnosis, histopathologic type, and other tumor markers. All patients with this tumor should be considered for entry into clinical trials [47].

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Family Medicine
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Diseases of the Prostate

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1 General Principles

The diseases of the prostate discussed in this chapter, except for a commonality that they occur in the prostate gland, represent a heterogeneous group of conditions with overlapping symptoms. The incidence of these conditions varies considerably by age. Benign prostatic hypertrophy (BPH) and lower urinary tract symptoms (LUTS) generally affect older men; younger men are at higher risk of acute prostatitis, and prostate cancer peaks in men aged 65–74. Because they represent distinct clinical entities, except for BPH and LUTS, these conditions will be presented separately.

2 Benign Prostatic Hypertrophy (BPH) and Lower Urinary Tract Symptoms (LUTS)

2.1 Definition, Background, and Classification

Benign prostatic hypertrophy (BPH) is an age-related condition characterized by proliferation of the smooth muscle and epithelial cells within the prostatic transition zone. The presence of BPH does not imply that patients will have symptoms or complications due to this condition. The etiology remains unknown.

The term lower urinary tract symptoms (LUTS) allows for a broad description of urinary symptoms in a population of older men without identification of a specific disease-based etiology [1]. The most common cause of LUTS is BPH, but the relationship between BPH and LUTS is complex. The term LUTS independent of BPH has been introduced and is gaining worldwide acceptance, although LUTS secondary to BPH is a clinically useful term. LUTS can be associated with other comorbidities including renal insufficiency, bladder calculi, and urinary incontinence.

The presence of BPH contributes to LUTS in at least two ways. Direct bladder outlet obstruction from enlarged tissue represents a static component, while increased smooth muscle tone and resistance within the enlarged gland itself represent a dynamic component. Thus, BPH, LUTS, and direct bladder outlet obstruction are all inextricably related. Finally, BPH and LUTS can be associated with other comorbidities including acute urinary retention, renal insufficiency, hematuria, bladder calculi, urinary incontinence, and recurrent urinary tract infections.

Older literature tended to separate out these clinical conditions, but heterogeneity in defining BPH and LUTS makes validation across study populations difficult for the purpose of classification. Therefore, consistent with newer literature, these conditions will be discussed together as part of a spectrum of disorders rather than distinct entities.

2.2 Epidemiology

The incidence of BPH is age related. In general, most men who live long enough will develop some form of BPH, with estimated incidences of up to 90 % in men over 70. The incidence of LUTS varies across

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epidemiologic studies. Up to 60 % of men experience symptoms after the age of 40, and by age 80 this increases to 70 % [2]. Since the number of people older than 80 is expected to rise considerably, from 9.3 million in 2000 to a projected 19.5 million by the year 2030 [3], the prevalence of LUTS and BPH will increase sharply in the near future.

2.3 Approach to the Patient

Men with symptoms of LUTS may not bring these to the attention of their family physician, dismissing these symptoms as a normal consequence of aging. Although it may be tempting for the physician to act similarly, LUTS is associated with a significant prevalence of urinary tract infections, bladder stones, urinary retention, and to a lesser extent acute renal failure. Men with LUTS also report impairment of disease-specific quality of life including sexual dysfunction; consequently, this condition will have an impact on family members and caretakers as well. Men with severe LUTS also have an increased risk of falling.

Neither the American Academy of Family Physicians nor the US Preventive Services Task Force makes recommendations regarding screening for LUTS or BPH [4]. Although no evidence exists that patient-oriented outcomes are improved by screening for this condition, since men may not bring symptoms of this condition to their physician's attention, and given that LUTS is associated with certain poor patient outcomes and the condition is prevalent, the family physician should consider including questions about LUTS in a general review of symptoms.

3 Diagnosis

3.1 History

Most patients with problems caused by BPH and LUTS present with symptoms of dysfunctional voiding.

These symptoms include urinary frequency, decreased force and caliber of the urinary stream, hesitancy, straining, urgency, and nocturia. Additionally, LUTS should be suspected in men with frequent UTIs and symptoms of the other complications of LUTS (see below in differential diagnosis). Severity of dysfunctional voiding will range from minimal to frank urinary retention.

In our "information age," urologic drugs and alternative drugs are heavily advertised on television. Coupled with the proliferation of medical information on the Internet, patients may become aware of and present with symptoms they discovered through these resources. For example, the website of the official foundation of the American Urological Association, available to anyone with Internet access, lists the following symptoms of LUTS [5]:

- The need to frequently empty the bladder, especially at night
- Difficulty in beginning to urinate
- Dribbling after urination ends
- Decreased size and strength of the urine stream
- Sensation that the bladder is not empty, even after a man is done urinating
- Inability to postpone urination once the urge to urinate begins
- Pushing or straining in order to urinate

Evaluation of LUTS symptoms is easier if clinicians use a standardized and validated tool, the most common being the International Prostate Symptom Score (IPSS) derived from the American Urological Association (AUA) score from the early 1990s (Fig. 1, IPSS). This seven-item self-administered questionnaire allows the clinician to address subjective symptoms in an organized manner. By adding

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The International Prostate Symptom Score (I-PSS)

Patient Name: _____ Date of birth: _____

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	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	1time	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	

Quality of life

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

The first seven questions of the I-PSS are identical to the questions appearing on the American Urological Association (AUA) Symptom Index which currently categorizes symptoms as:

Mild (symptom score ≤ 7)
Moderate (symptom score range 8-19)
Severe (symptom score range 20-35)

The International Scientific Committee (SCI), recommends the use of only a single question to assess the quality of life. The answers to this question range from "delighted" to "terrible" or 0 to 6. Although this single question may or may not capture the global impact of benign prostatic hyperplasia (BPH) Symptoms or quality of life, it may serve as a valuable starting point for a doctor-patient conversation.

Adapted from http://www.urospec.com/uro/Forms/ipss.pdf accessed 122714

Fig. 1 The International Prostate Symptom Score (IPSS) (Adapted from http://www.urospec.com/uro/Forms/ipss.pdf. Accessed 27 Dec 2014)

the scores with equal weighting to the questions, a summary score is generated which has been shown to be an accurate reflection of a man's overall symptoms over the preceding month.

Care should be taken while interpreting the IPSS. Men report nocturia with accuracy but tend to overstate daytime frequency. Men with low educational status are more likely to misunderstand the IPSS and tend to misrepresent their symptoms and may receive inappropriate treatment. When administered by a medical professional, many of the inaccuracies disappear, even though the questionnaire is recommended as "self-administered." There are other questionnaires that may capture more patients with LUTS, such as the Core Lower Urinary Tract Symptom Score (CLSS), but the IPSS is recommended (level 2 evidence, Grade C recommendation) [6].

Note that besides the seven symptom questions, there is a final question where patients estimate the overall effect of LUTS symptoms on their quality of life. This last question is used independently as a factor in deciding on the appropriate level of therapy. It is sometimes referred to as a "bother score" in some literature.

A detailed medical history should be obtained to identify other causes of voiding dysfunction or comorbidities that may complicate the treatment.

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3.2 Physical Examination

Along with a general physical examination, a digital rectal examination (DRE) and focused neurologic examination should be performed. DRE provides a relatively crude estimate of prostate size when compared with measurements using transrectal ultrasonography or magnetic resonance imaging, but has positive predictive value of 94 % in identifying prostate above 30 cc [7], and is recommended as part of the work-up by the AUA. Nodules and other indications of prostate cancer may also be discovered by this exam and on occasion will change the evaluation and treatment of men with LUTS symptoms.

3.3 Laboratory and Imaging

A urinalysis (UA) should be ordered in all patients to evaluate for a non-BPH pathologic process as a cause of symptoms. Urinalysis assists in distinguishing urinary tract infection (UTI) and bladder cancer from BPH (if cytology is ordered). Other conditions, such as diabetes, may also be uncovered by the UA. The positive predictive value of the UA to detect serious urinary tract disorders, which are relatively uncommon, is low, but given that the UA is noninvasive and inexpensive, its use is valid. Urine cytology should be considered when symptoms include severe irritable symptoms and dysuria, especially if there is a smoking history.

Prostate-specific antigen (PSA) testing is controversial since the presence of BPH can increase PSA levels and cause confusion and unnecessary testing [8]. The AUA recommends PSA testing when life expectancy is greater than 10 years and if the diagnosis of prostate cancer can modify the management. The National Institute for Health and Care Excellence (NICE) guidelines from Britain suggest that men should be asked if they wish to have PSA testing if symptoms are suggestive of bladder outlet obstruction secondary to BPH, their prostate feels abnormal on DRE, or they are concerned about prostate cancer [9]. In the absence of prostate cancer, the PSA provides a guide to prostate volume and is an indication of the likelihood of response to therapy with 5α-reductase inhibitors.

3.4 Special Testing

Routine cystoscopy, imaging of the upper urinary tract, flow rate measurement, post-void residual volume measurement, serum creatinine measurement, and prostate imaging with transabdominal or transrectal ultrasound are not routinely recommended. These and other tests can be used if there is clinical suspicion that these tests will rule out alternative diagnoses, alter treatment, or change specific outcomes.

Voiding diaries are simple and inexpensive and may provide useful objective clinical information. There is a close correlation between LUTS, as assessed by symptom scores, and data generated by voiding charts.

3.5 Differential Diagnosis

There are many things that cause some of the symptoms of LUTS. These include but are not limited to:

- Prostate cancer, bacterial prostatitis, prostatic abscess
- UTI
- Medications: opiates, decongestants, antihistamines, tricyclic antidepressants
- Bladder cancer, neurogenic bladder, overactive bladder, bladder foreign bodies
- Urethral strictures
- Diabetes and other medical conditions that cause nocturia or polyuria

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4 Treatment

Patients with mild degrees of bother (IPSS < 8) and small glands or patients with moderate to severe symptoms (IPSS ≥ 8) who are not bothered by their LUTS may be managed with watchful waiting and lifestyle modifications. Patients with more severe symptoms or bother can be offered medical therapy. Surgical therapy is reserved for patients who fail medical therapy or have complications. Sexual dysfunction can be an associated symptom and should be addressed (see chapter "► Care of the Obese Patient"). Watchful waiting does not imply the total absence of intervention. Patients should be followed closely and monitored for response to therapy and complications of LUTS.

4.1 Behavioral

Symptoms of LUTS can be improved with patient-instituted behavioral interventions. These include timed voiding schedules, decreasing fluid intake before bedtime, avoiding certain spicy foods and caffeine, smoking cessation, and moderating alcohol consumption. Pelvic floor exercises can be helpful, as is treating constipation. Stopping or reducing dosages of diuretics and other medications that adversely affect the bladder and bladder training may all improve LUTS.

4.2 Medications

Two classes of drugs are used to treat BPH and LUTS: α-adrenergic blocker and 5α-reductase inhibitors. α-Adrenergic blocker has a strong physiologic basis for their effectiveness. Smooth muscle tone of the prostate is mediated by α-receptors, and increased smooth muscle tone leads to a reduction in urinary flow rate and worsening symptoms of LUTS. The other class, 5α-reductase inhibitors, works by blocking the conversion of testosterone to its metabolite, dihydrotestosterone (DHT). DHT promotes growth of the prostate. When DHT absorption into the prostate has been reduced, which takes 3–6 months, the prostate shrinks and symptoms of BPH and LUTS are improved.

α-Adrenergic blockers are considered first-line therapeutic option for men with symptoms who desire treatment (level 1 evidence, Grade A recommendation) [6]. Alfuzosin, doxazosin, tamsulosin, and terazosin are the available drugs. They do not alter the natural progression of the disease. These drugs can be considered equally effective though they have varying side effect profiles. Unfortunately, these medications may aggravate sexual dysfunction associated with LUTS.

Several studies have demonstrated that 5α-reductase inhibitors (dutasteride and finasteride), in addition to improving symptoms, can reduce the risk of acute urinary retention secondary to BPH and the need for surgical intervention (level 1 evidence, Grade A recommendation) [10]. Men with small prostates, less than <40 mL, are less likely to benefit from finasteride.

Prognostic factors suggesting the potential for BPH risk progression include:

- Serum PSA >1.4 ng/mL
- Age >50
- Gland volume >30 cc

Combination therapy with α-adrenergic blocker and 5α-reductase inhibitors can be considered if LUTS is associated with prostatic enlargement. Improved symptom score and peak urinary flow rates are improved when compared to monotherapy when either drugs are used alone. Combination therapy is associated with decreased risk of urinary retention or prostate surgery. α-Adrenergic blocker may be discontinued after 6–9 months of therapy if symptoms improve.

Anticolinergics may be used cautiously in patients that have bladder overactivity, but should be avoided in patients with overactive elevated residual urine volume.

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The PDE5 inhibitors, such as sildenafil, vardenafil, and tadalafil, have shown improvement in symptoms and quality of life in men with LUTS and erectile dysfunction and should be considered if appropriate. There is no recommendation to use these drugs unless the patient had erectile dysfunction.

Effectiveness of phytotherapies (e.g., saw palmetto, African plum) is not supported by evidence [11].

4.3 Referrals

Acute urinary retention is often indicative of end-stage bladder decompensation and is an indication for surgical referral. Referral should also be considered in patients with severe LUTS who either fail medical treatment or do not want medical therapy. These treatments include monopolar transurethral resection of the prostate (TURP), laser prostatectomy, transurethral microwave therapy, transurethral needle ablation, and stents. A discussion of these therapies is beyond the scope of this article. The family physician should inform their patients that these treatments can have significant side effects that are procedure dependent. These complications include but are not limited to operative bleeding severe enough to require transfusion, infection, and the need for further procedures at some point in the future. Possible postoperative complications affecting sexual function include retrograde ejaculation (occurring in approximately one-third of patients) and impotence or erectile dysfunction not present preoperatively.

4.4 Patient Education

Patient education centers around behavioral treatments described above. Additionally, since there is little evidence that any dietary supplement, combination of phytotherapeutic agents, or other nonconventional therapy is effective for the management of BPH/ LUTS, and these treatments can be expensive, the family physician may consider counseling patients against pursuing these treatments. Finally, patients who elect to pursue a watchful waiting treatment plan should be reevaluated at 6 months. Additionally, patients should be educated on the non-pharmacologic treatments that help:

- Fluid restriction particularly prior to bedtime
- Avoidance of caffeinated beverages and spicy foods
- Avoidance/monitoring of some drugs (e.g., diuretics, decongestants, antihistamines, antidepressants)
- Timed or organized voiding (bladder retraining)
- Pelvic floor exercises
- Avoidance or treatment of constipation

5 Prevention

There is no good evidence for any specific primary preventions for BPH, but some literature suggests that weight loss, regular physical activity, vegetable consumption, and reduction of fatty food can reduce the risk of developing BPH. Since these recommendations are in keeping with general good health, patients should undertake these behaviors.

6 Family and Community Issues

There is a clear relationship between LUTS due to BPH and erectile dysfunction. As symptoms increase, there is associated higher rate of sexual dissatisfaction. While there are no studies that directly address this issue, family physicians should consider this and discuss sexual function even if the patient does not

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volunteer this information. Additionally, men may be embarrassed about this condition and might even be pushed to discuss this issue by their spouses.

7 Prostatitis

7.1 General Principles

The term prostatitis encompasses a group of common conditions that are distinct but interrelated clinical entities such as acute bacterial prostatitis, chronic bacterial prostatitis, chronic prostatitis/chronic pelvic pain syndrome, and asymptomatic prostatitis, and all have varying clinical significances, etiologies, treatment plans, and long-term prognoses.

The National Institute of Health (NIH) consensus classification will be used to separate these conditions into their different categories for purposes of discussion. Limited research exists to guide the diagnosis and management of these entities, making prostatitis a challenging condition to manage.

7.2 Definition/Background

The National Institute of Health/National Institute of Diabetes and Digestive and Kidney Diseases classification of prostatitis syndromes is the most accepted classification system. This categorized prostatitis syndromes into four classes with two subclasses [12] (Table 1):

7.3 Epidemiology

The exact incidence of prostatitis is unknown, although it is a common disorder with an estimated incidence in one study of approximately 9.7 % [13]. Though acute prostatitis is often considered a disease of younger men (aged 35–50 years), it does occur in older men as well. Acute and chronic bacterial

Table 1 NIH prostatitis classification

Category	Designation	Description
I	Acute bacterial prostatitis	Acute infection of the prostate gland
		Recovery of bacteria from prostatic fluid
		Purulence of fluid
		Systemic signs of infectious illness (fever, chills, myalgias)
II	Chronic bacterial prostatitis	Chronic infection of the prostate gland
		Recovery of bacteria in significant numbers from prostatic fluid in the absence of concomitant urinary infection
		No significant systemic signs (as in acute bacterial prostatitis)
III	Chronic nonbacterial prostatitis/chronic pelvic pain syndrome (CPPS)	No demonstrable infection
IIIA	Inflammatory	WBC in semen/EPS/post-prostatic massage urine
		Leukocytes in semen, expressed prostatic secretions, or post-prostatic massage urine
IIIB	Noninflammatory	No leukocytes in semen, expressed prostatic secretions, or post-prostatic massage urine
IV	Asymptomatic inflammatory prostatitis	Patients present with BPH, elevated PSA level, prostate cancer, or infertility
	By definition the patient has no symptoms	Microscopy of EPS or semen and/or histologic examination of BPH chips, prostate cancer specimens, or prostate biopsy specimens disclose evidence of prostatic inflammation

WBC white blood cell, *EPS* expressed prostatic secretion, *BPH* benign prostatic hypertrophy/lower urinary tract symptoms

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prostatitis affects less than 5 % of men with prostatitis. Most patients with prostatitis are found to have either nonbacterial prostatitis or inflammatory prostatitis. When evaluating a patient with symptoms of prostatitis, it is important to classify the condition according to the NIH system since treatment options vary with the condition. Approximately 5 % of patients with acute bacterial prostatitis may progress to chronic bacterial prostatitis.

7.4 Acute Bacterial Prostatitis (ABP: Category I)

7.4.1 Approach to the Patient

Acute bacterial prostatitis, category I (ABP), is an often generalized infection. Patients are generally very ill and may be septic. ABP in most patients probably originates from ascending urethral infections and probably results from the reflux of infected urine into the ejaculatory and prostatic ducts that empty into the posterior urethra. ABP may develop in patients after initial prostate biopsy despite pre-procedural prophylactic antibiotic administration.

7.4.2 Diagnosis

History Men present with dysuria, frequency, and suprapubic, pelvic, or perineal pain with variable voiding symptoms. Fever, chills, malaise, nausea, and vomiting are common. Elderly men may have acute mental status changes. Bladder neck spasm may result in urinary retention and is seen in around one-fifth of patients.

Other contributing historical factors include sexual history, history of sexually transmitted diseases or urethritis, coexisting medical problems, and a history of prior prostate procedures and inguinal or pelvic surgery.

Physical Evaluation consists of a complete physical examination, with special attention to the abdominal, genital, and perineal areas. A gentle digital rectal examination should be performed – with a vigorous digital rectal examination, there is a theoretical risk of systemic bacterial dissemination. The prostate is very tender, enlarged, and boggy. A palpable, distended bladder may indicate urinary retention. Other aspects of the physical may be indicative of a general septic state.

Laboratory and Imaging and Special Testing A urinalysis and midstream culture should be obtained in all patients. The presence of more than ten white blood cells per high-power field suggests a positive diagnosis. Other laboratory testings – CBC, electrolyte levels, and blood culture – should be ordered if indicated by the severity of the presentation. Residual urine should be documented by ultrasound if a patient has a palpable bladder or urinary retention is suspected. Serum C-reactive protein is usually elevated and may be obtained if a septic picture is present. Because increased vascular permeability and disrupted epithelium of the prostate gland cause leakage of PSA, checking a PSA is not indicated since levels are usually elevated. If elevated, PSA levels will normalize following treatment, and failure to do so may indicate concurrent prostate cancer. CT scanning is indicated if considering the need to diagnose and drain prostatic or pelvic abscess or for ruling out other pelvic pathology-mimicking prostatitis.

7.4.3 Treatment

Medication Acute prostatitis can be considered a medical emergency. Patients with suspected sepsis or who are severely ill should be hospitalized and treated with parenteral antibiotics. Supportive therapy – fluids, analgesics, and antipyretics – is ordered as indicated. Short-term urethral catheterization may be necessary if there is urinary retention, but carries with it the theoretical risk of bacteremia, especially with traumatic catheterization.

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Initiation of empirical antibiotics is important prior to obtaining culture results. The most common cause of acute prostatitis is the *Enterobacteriaceae* family of gram-negative bacteria, which originates in the gastrointestinal flora. *Escherichia coli* is the most common, but other gram-negative organisms, such as *Klebsiella*, *Proteus*, and *Pseudomonas*, and gram-positive *Enterococcus* species are often isolated as well. Empiric antibiotic therapy should be directed at these organisms with consideration of local sensitivity patterns.

For hospitalized patients, useful agents include combination of penicillin (ampicillin) and an aminoglycoside (gentamicin), second- or third-generation cephalosporins (ceftriaxone, cefotaxime), or a fluoroquinolone (ciprofloxin, levofloxin). Aminoglycosides should be avoided in patients with preexisting renal disease.

Less ill patients may be treated as an outpatient with careful follow-up. Fluoroquinolones are recommended as first-line agents. Compared with concentrations in plasma, drug levels are generally higher in urine, similar in seminal fluid and prostatic tissue, and lower but therapeutic in prostatic fluid. Unfortunately, antibiotic resistance to fluoroquinolones is increasing, and local resistance patterns should be considered when planning therapy.

Patients with acute prostatitis secondary to manipulation have a higher risk of prostate abscess and frequency of multiple infections, with causative organisms other than *E. coli*. Consequently, these men may require modified treatment.

When the acute phase of infection settles down, therapy should be continued with one of the oral antimicrobial agents appropriate for the treatment of chronic bacterial prostatitis (see below). The duration of optimal therapy is unknown, but between 2 and 4 weeks has been suggested [14].

In addition to antibiotic therapy, nonsteroidal anti-inflammatory drugs (NSAIDs) may offer both analgesia and more rapid healing through liquefaction of prostatic secretions.

Sexually transmissible infections such as chlamydia and gonorrhea should be considered, particularly in young men. If chlamydia is thought to be the causative agent, azithromycin 1 g orally stat or doxycycline 100 mg orally twice daily for 7 days is appropriate. If gonorrhea is suspected, ceftriaxone 500 mg intramuscularly and azithromycin 1 g orally are indicated.

Referral Urologic consultation should be obtained in patients with urinary obstruction or other complications that require intervention, such as suspected abscess formation. Infectious disease consultation is indicated for unusual causative organisms, immunocompromised patients, or those who do not respond to initial therapy.

7.4.4 Prevention

Certain conditions, such as diabetes mellitus and promiscuous sexual activity, may predispose to the development of acute prostatitis. Control of diabetes and safe sex practices theoretically decrease the incidence of this condition.

7.5 Chronic Bacterial Prostatitis (CBP: Category II)

CBP is caused by chronic bacterial infection of the prostate, with or without prostatic symptoms. Patients may be asymptomatic and have incidentally noted persistent or recurrent bacteriuria or may present with recurrent urinary tract infection associated with classic symptoms such as frequency, dysuria, urgency, perineal discomfort, and a low-grade fever.

7.5.1 Approach to the Patient

The symptoms of CBP (NIH category II) cannot be distinguished from those of CP/CPPS (NIH category III), and the evaluation must determine which condition exists. Chronic prostatitis is essentially a

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diagnosis of exclusion. The evaluation should exclude other possible causes for the patients' symptoms such as benign prostatic hyperplasia, urethral stricture, and urinary infection. Sexual dysfunction may accompany chronic bacterial prostatitis, although it does not clearly occur more commonly than in men of a similar age without prostatitis.

7.5.2 Diagnosis

History Symptoms of CP/CPPS can vary widely and include pain in the perineum, lower abdomen, testicles, and penis and with ejaculation, bladder irritation (irritative symptoms during micturition), bladder outlet obstruction, and sometimes blood in the semen. Additional symptoms include erectile dysfunction and loss of libido. The patient may be free of symptoms between the episodes. Recurrent infections of the urinary tract with the same pathogen are typical. A patient may also have a history of urethritis, epididymitis, and distal penile pain.

Physical Examination The physical exam may be normal or nonspecific. Important aspects of the physical exam include the abdominal examination followed by careful examination and palpation of the groin, spermatic cord, epididymis,, and testes. The clinician is looking for areas of pain or discomfort, for masses, and for urinary retention. A digital rectal examination evaluates the prostate for tenderness or discomfort, consistency, nodules, and irregularities.

Laboratory and Imaging A urine analysis and culture should be ordered. For patients with recurrent symptoms, the culture often yields repeated isolation of the same organism. The diagnosis of CBP is made with either a four-glass test (initial urine, midstream urine, expressed prostatic secretion, urine after prostatic massage) or with a two-glass test (midstream urine and post-prostatic massage urine). The impracticality of the four-glass test limits its usefulness. The two diagnostic methods can be regarded as clinically equivalent.

Diagnostic criteria for CBP are:

- Bacterial count in the prostatic secretion and/or in the post-prostatic massage urine should be tenfold greater than in midstream urine.
- $\geq 10/mm^3$ in post-prostatic massage urine or $\geq 10/1{,}000 \times$ expressed prostatic secretion.
- Leukocytes or noncellular markers of inflammation (e.g., leukocyte esterase or interleukin-8) must be detected in prostatic secretion and/or in post-prostatic massage urine.
- Leukocytes in ejaculate are $>10^6$ PPL/mL (the test for leukocytes in ejaculate must be performed with special stains (e.g., peroxidase stain), to distinguish leukocytes microscopically from the precursors of spermatozoa).
- Bacteria in the ejaculate alone are not adequate, as the microbiological findings only agree with the results of the two-glass or four-glass tests in about half the cases.

Practical details of the two-glass test: The patient provides a midstream pre-massage urine specimen. The physician performs prostatic massage, and a second urine specimen (initial 10 mL) is obtained. Microscopy and culture of the two screening urine specimens allow the categorization of the majority of patients presenting with a chronic prostatitis syndrome.

Urine culture 48 h posttreatment is useful combined with reevaluation after 7 days of antibiotic treatment to assess clinical response.

Prostate-specific antigen (PSA) testing is not recommended. All forms of prostatitis may falsely elevate the PSA, and a return to normal levels does not rule out prostate cancer. Consequently, testing the PSA in

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this context is essentially prostate cancer screening (see below) and should be discussed carefully with the patient.

Special Testing Special testing is not required for the diagnosis of CBP. If patients have symptoms of obstruction, urodynamic or post-void residual determinations are useful. If patients do not respond to treatment cystoscopy or other urodynamics, studies may be indicated.

The NIH Chronic Prostatitis Symptom Index from the Chronic Prostatitis Collaborative Research Network (CPCRN) is a validated questionnaire (available at http://www.prostatitis.org/symptomindex.html) that can quantify symptoms and help monitor response to treatment. It is an easily self-administered and highly discriminative test.

Sexually active men younger than 35 years and older men who engage in high-risk sexual behaviors should be tested for *Neisseria gonorrhoeae* and *Chlamydia trachomatis*.

Differential Diagnosis LUTS may mimic chronic prostatitis. Chronic lower urinary tract symptoms in young men are often misdiagnosed as chronic nonbacterial prostatitis when in fact they may have undiagnosed chronic voiding dysfunction. Prostate cancer, though usually asymptomatic, may present with symptoms of CBP. Other conditions to consider are stones or foreign body within the urinary tract, bladder cancer, prostatic abscess, and enterovesical fistula.

7.5.3 Treatment

There is considerable overlap between CBP and chronic nonbacterial prostatitis/chronic pelvic pain syndrome (CPPS – class IIIa and class IIb) discussed in the next section. In this section, recommendations for treating CBP category II are emphasized.

Behavioral Changes to daily activities and dietary changes do not have a prominent role in the treatment. Some physicians have advocated the avoidance of spicy and caffeine-containing foods; however, no evidence has indicated any benefit. Sitz baths and perineal massage may help with discomfort.

Medications A trial of antibiotic therapy is an initial treatment. Fluoroquinolones penetrate relatively well into the prostate and are the therapy of choice. Trimethoprim/sulfamethoxazole may be considered, but tissue penetration is less effective, and there may be local resistance. If cultures (urine, EPS, semen) are positive, or the patient notices significant clinical improvement, a total treatment period of 4–6 weeks is recommended. In culture-negative prostatitis, antibiotics should be discontinued after 2 weeks in the absence of clinical improvement. Second-line drugs include doxycycline, azithromycin, and clarithromycin.

The alpha-blockers can help to decrease recurrences by diminishing urinary obstruction due to prostate enlargement or congestion secondary to inflammation. Combination treatment with α-blockers (tamsulosin, terazosin, or alfuzosin) and antibiotics shows a higher cure rate than antibiotics alone. Men with more severe symptoms are significantly more likely to respond. Treatment with an α-blocker for 3–6 months is reasonable but lacking in good-quality evidence. Nonsteroidal anti-inflammatory drugs (NSAIDs) can provide some relief.

If repetitive courses fail and the patient has improved symptoms while on antibiotics, consider long-term, low-dose, suppressive therapy, especially if cultures remain positive. Medications to consider include trimethoprim/sulfamethoxazole or a fluoroquinolone.

Referrals Urology consultation may help in patients that do not respond to treatment or if a more complex differential diagnosis is considered. Surgery is usually not indicated, though some procedures

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have a limited role. Patients with primary bladder neck obstruction who fail medical therapy may benefit from transurethral incision of the prostate. Other procedures may be indicated depending on the coexistent conditions and are best managed by a urologist. Aggressive surgeries for chronic prostatitis generally cause more problems and lack solid evidence to support their use.

Counseling and Patient Education This will be discussed as part of patient education of chronic nonbacterial prostatitis/chronic pelvic pain syndrome (NIH class III).

7.6 Family Issues

As mentioned above, this condition is associated with sexual dysfunction and will often have an impact on the patient's spouse, who may also either push the patient for treatment or even mention this condition in a visit of her own without the husband present.

7.7 Chronic Nonbacterial Prostatitis/Chronic Pelvic Pain Syndrome (CPPS: Class IIIa and Class IIb)

7.7.1 General Principles

This condition is more common than either acute bacterial or chronic bacterial prostatitis. The etiology is poorly understood. Inflammatory and infectious causative mechanisms have been proposed, although there is poor correlation between the amount of inflammation within the prostate gland itself and the degree of symptoms. Psychological stress may be a major contributor to symptom severity, and there may be an association between irritable bowel syndrome, chronic fatigue syndrome, and fibromyalgia.

7.7.2 Approach to the Patient

Diagnosis is essentially one of exclusion. The diagnosis of ABP and CBP should be considered and eliminated.

7.7.3 Diagnosis

History Symptoms of CP/CPPS can vary widely and are similar to those of CBP listed above. In most patients, the dominant symptom is pain concentrated in the anorectal and genital areas, but may also affect the entire pelvis. Other symptoms include bladder irritation, bladder outlet obstruction, erectile dysfunction, and hematospermia. Quality of life may also be affected and includes symptoms of depression. Diagnosis requires the patient to have had pelvic pain or urinary symptoms for more than three of the previous 6 months with no evidence of ABP or urinary tract infection in that time [15].

Physical Examination The physical exam is the same as for CBP.

Laboratory, Imaging, and Special Testing A urinalysis and midstream culture should be obtained on all patients. Since leukocytes and bacterial counts do not directly correlate with symptoms, and these abnormalities often present in asymptomatic patients, the utility and importance of this test are limited. The two-glass test can help rule out CBP (NIH class II).

No other tests or imaging is necessary. Since chronic prostatitis/chronic pelvic pain syndrome is a diagnosis of exclusion, additional laboratory or imaging studies are used to rule out other causes of the patients' symptoms and should only be ordered when other diagnoses are considered after a careful history and physical examination. Of note, an elevated PSA should not be attributed to CP/CPPS and warrants further investigation.

Symptoms should be validated with the standard questionnaire of the National Institute of Health Chronic Prostatitis Symptom Index (NIH-CPSI). This questionnaire quantifies symptoms related to pain,

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micturition, and quality of life. Changes in the overall score from baseline of six points correlate with the therapeutic response and can be used to guide therapy.

If there is evidence for obstructive symptoms, uroflowmetry and evaluation of post-void residual are useful. Cystoscopy, CT, or MRI of the prostate are not recommended.

Differential Diagnosis The differential diagnosis is similar to ABP and CBP. The physician should consider diseases of the rectum, the external genitals, the urethra, and the bladder, since the nerves of other pelvic organs may interact with prostatic innervation.

7.7.4 Treatment

Treatment will have to be individualized. Treating this condition may be frustrating for the family physician because guidance in the form of good-quality evidence is lacking: The current understanding of CP/CPPS is not complete enough to determine appropriate interventions for all patients [16].

Behavioral Voiding and pain symptoms associated with CP/CPPS may be secondary to some form of pseudodyssynergia during voiding or repetitive perineal muscle spasm. Some small uncontrolled studies have shown that biofeedback can improve symptoms [17]. Physical therapy and pelvic floor training may help improve symptoms. If depression or anxiety is associated with this condition, treatment with selective serotonin reuptake inhibitor (SSRI) antidepressants can be prescribed.

Medications/Immunizations and Chemoprophylaxis There is no evidence-based or specific treatment for this condition. Of the treatments that have been studied, alpha-adrenergic receptor blockers and antibiotics alone or in combination appear to have the greatest improvement in symptom scores when compared with placebo. Anti-inflammatory medications may also be useful for patients presenting with pain [Grade 2, level C evidence] [18]. When alpha-blockers are used, therapy for at least 6 months is recommended, as this leads to downregulation of the alpha-receptors in the prostate.

Additional therapies such as muscle relaxants (if there is evidence for functional abnormalities in the pelvic floor) and intraprostatic injection of botulinum toxin A are being investigated and may offer additional therapies, but definitive evidence is lacking.

If a patient does not respond to treatment, repeated trials are not warranted. In addition, it is important to consider multimodal therapy with a combination of medications or possible adjunctive therapy with non-pharmacologic modalities. Physical therapy aimed at achieving myofascial trigger point release, performed by a physical therapist, may have benefit in patients with pelvic floor muscle spasm.

Referrals Men with this condition represent a highly complex group of patients, and urology referral is often necessary. One study of patients refractory to medical treatment found that transurethral intraprostatic injection of botulinum neurotoxin type A reduced pain and improved quality of life. By 6 months after treatment, pain had decreased almost 80 % from baseline in the treated group [19].

Counseling CP/CPPS is associated with depression and a poor quality of life. Psychologist referral should be considered in select patients with concomitant psychosocial problems. A cognitive behavioral program specifically targeting CP/CPPS can improve both symptoms and quality of life [20]. This approach addresses pain, urinary difficulties, depressive symptoms, social support, sexual functioning, and overall quality of life issues.

7.7.5 Prevention

There is no known prevention of this condition.

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7.8 Family and Community Issues

Since sexual functioning depression and behavioral issues are common in this condition, appropriate other family members may need to be involved in care plans and counseling.

7.9 Asymptomatic Inflammatory Prostatitis (AIP Class: IV)

By definition, this condition does not cause symptoms. It is diagnosed when inflammatory cells are identified on prostate biopsy. These patients may have presented with BPH, an elevated PSA level, prostate cancer, or infertility. The clinical significance of this condition is uncertain, and treatment is based on the primary reason for the urologic evaluation. When the indication for biopsy is an elevated PSA level, it is important to remember that normalization of the PSA value after antibiotic or 5-alpha-reductase inhibitor therapy does not rule out the diagnosis of prostate cancer, and continued urologic evaluation is warranted.

8 Prostate Cancer

8.1 General Principles

The family physician will usually be more involved in shared decision making regarding screening than in the treatment of prostate cancer. Unfortunately, screening for prostate cancer, threshold levels for prostate-specific antigen (PSA) levels to guide diagnosis and treatment, and the best treatment for diagnosed prostate cancer remain controversial. This places the family physician in the awkward position of interpreting conflicting evidence and recommendations from learned societies when trying to appropriately advise patients. Testosterone is required for the maintenance of a normal, healthy prostatic epithelium and a prerequisite for the development of prostate cancer.

Recommendations of major related organizations regarding screening can be summarized as follows:

The American Academy of Family Physicians (AAFP) and the US Preventive Service Task Force (USPSTF) recommend against screening for prostate cancer, giving it a D recommendation [21, 22].

The *American Urologic Association (AUA)* released a new guideline in 2013 writing that "Men ages 55 to 69 are urged to talk with their doctors about benefits, harms of testing." The AUA recommendation continues, writing: "For men ages 55 to 69 years, the decision to undergo PSA screening involves weighing the benefits of preventing prostate cancer mortality in 1 man for every 1,000 men screened over a decade against the known potential harms associated with screening and treatment. For this reason, shared decision making is recommended for men age 55 to 69 years that are considering PSA screening, and proceeding based on patients' values and preferences" [23].

In a recent review of evidence published in March of 2014 in the Journal of the American Medical Association (JAMA), the authors write: "Available evidence favors clinician discussion of the pros and cons of PSA screening with average-risk men aged 55 to 69 years. Only men who express a definite preference for screening should have PSA testing. Other strategies to mitigate the potential harms of screening include considering biennial screening, a higher PSA threshold for biopsy, and conservative therapy for men receiving a new diagnosis of prostate cancer" [24].

Finally, *the **American Cancer Society*** writes: "Starting at age 50, men should talk to a doctor about the pros and cons of testing so they can decide if testing is the right choice for them. If they are African American or have a father or brother who had prostate cancer before age 65, men should have this talk with a doctor starting at age 45. If men decide to be tested, they should have the PSA blood test with or without a rectal exam. How often they are tested will depend on their PSA level" [25].

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A rational approach can be based on the JAMA recommendations which read: "Because trials have not directly compared different approaches, a reasonable strategy is to inform and involve men not only in the decision whether to screen but also in any subsequent decisions about biopsy and treatment."

8.1.1 Definition/Background

Prostate cancer generally refers to adenocarcinoma originating in the prostate gland. Recommendations regarding this disease change rapidly, so the family practitioner should follow the latest recommendations regarding screening, diagnosis, and treatment of this common condition.

8.1.2 Epidemiology

The lifetime risk of dying of prostate cancer is less than 3 %. About 2 % of all prostate cancer deaths occur before the age of 55 years, 28 % occurring between ages 55 and 74 years and 70 % at age 75 years or older [26]. African American ethnicity and family history in a first-degree relative receiving a diagnosis early in life are the primary risk factors for prostate cancer. Prostate cancer is rarely diagnosed in men younger than 50 years old. More than 75 % of men older than 85 years will have histological evident prostate cancer at autopsy, so it seems that most men who live long enough will get this disease, and this fact should be considered in any discussions regarding screening, diagnosis, and treatment. The incidence of prostate cancer among African Americans is nearly twice that observed among white Americans.

8.1.3 Classification

The Gleason score is used as a prognostic indicator and for planning treatment. This score is based on the sum of the two most common histologic patterns seen on each tissue specimen. In general, tumors are classified as well differentiated (Gleason score 2–6), of intermediate differentiation (Gleason score 7), or poorly differentiated (Gleason score 8–10). Cancer is also classified with regard to its extent (Table 2):

8.2 Approach to the Patient

Most patients with early-stage prostate cancer are asymptomatic. In a patient with symptoms, a thorough evaluation should be undertaken to rule out other causes of symptoms.

8.3 Diagnosis

The diagnosis of prostate cancer is usually made because of an elevated screening PSA level. A palpable nodule on digital rectal examination may prompt a biopsy and the diagnosis. Cancer is sometimes diagnosed as advanced disease because a patient presents with obstructive voiding symptoms, pelvic or perineal discomfort, lower-extremity edema, or bone lesions.

8.3.1 History

Most patients with early disease localized to the gland are asymptomatic. With advanced disease and growth into the urethra or bladder neck, for example, the patient may present with obstructive symptoms:

Table 2 TNM classification of prostate cancer

T1a	Nonpalpable, with 5 % of tissue with cancer, low grade (diagnosed by transurethral resection of the prostate)
T1b	Nonpalpable, with >5 % of tissue with cancer, high grade (diagnosed by transurethral resection of the prostate), or both
T1c	Nonpalpable, but prostate-specific antigen level elevated
T2a	Palpable, one-half of one lobe or less
T2b	Palpable, more than one-half of one lobe, not both lobes
T2c	Palpable, involves both lobes
T3a	Palpable, unilateral capsular penetration

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hesitancy, intermittent urinary stream, decreased force of stream, or hematuria and hematospermia. These symptoms are indistinguishable from symptoms of LUTS described above. Other symptoms of locally advanced disease are lower-extremity edema or discomfort in the pelvic and perineal areas.

Metastasis to the bone may be asymptomatic, but it can cause back pain, pathologic fractures, or spinal cord compression. Prostate cancer most often spreads to the bone, commonly leading to bone pain. Some patients develop spinal cord impingement from the epidural spread of disease, resulting in pain and neurologic compromise that could cause irreversible loss of bowel and bladder function and the ability to walk.

Patients may also present with lymphedema, renal insufficiency, or both as a consequence of obstruction of pelvic lymphatics and urethral outlet obstruction. Visceral metastasis is rare, and any number of symptoms related to the disease of these organ systems may occur.

8.3.2 Physical Examination

Routine digital rectal examination (DRE) as part of a wellness visit is controversial. No studies examined the independent role of screening by DRE [27]. As for men with symptoms suggestive of prostate disease, the DRE has a moderately low sensitivity and specificity for the diagnosis of prostate cancer, with values varying across studies. Walsh et al. discovered that DRE alone had a sensitivity and specificity of 81 % and 40 %, respectively, in diagnosing prostate cancer, with a positive predictive value of 42 % [28]. Since biopsy of a nodule or area of indurations reveals cancer about half the time, prostate biopsy should be undertaken in all men with palpable nodules, even if they have a normal PSA [29].

In patients with symptoms, a general physical exam based on the history will help exclude other causes of their symptoms including LUTS (see above).

8.3.3 Laboratory and Imaging and Special Testing

PSA should be ordered in men suspected of having prostate cancer or for screening if desired. There is no PSA level below which a man can be informed that prostate cancer does not exist. Rather, the risk of prostate cancer, and that of high-grade disease, is continuous as PSA increases [30]. For lower cut points such as 2.5–4.0 ng/mL, approximately 80 % of PSA tests will yield false-positive results. Though a cut point of 4.0 ng/mL has been the historic threshold, the PIVOT study suggests that the greatest benefit is realized when PSA levels are between 10 and 20 ng/mL [31].

Special imaging will depend on the suspected spread of the disease, intention of aggressive therapy, and factors discovered in the history and physical examination. Important considerations for the family physician are:

- Pretreatment serum PSA predicts the response of prostate cancer to local therapy.
- Routine use of a bone scan is not required for staging asymptomatic men with clinically localized prostate cancer when their PSA level is equal to or less than 20.0 ng/mL.
- Computed tomography or magnetic resonance imaging scans may be considered for the staging of men with high-risk clinically localized prostate cancer when the PSA is greater than 20.0 ng/mL or when locally advanced or when the Gleason score is greater than or equal to 8.

8.3.4 Differential Diagnosis

When symptomatic, the differential diagnosis of prostate cancer includes BPH and LUTS and the chronic prostatitis spectrum of disease described above. Other cancers of the abdomen can affect the bladder and bones, and consideration for other cancers is in the differential.

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8.4 Treatment

Treatment of prostate cancer diagnosed by PSA is controversial due in part to the lack of randomized controlled trials, and since the family physician will usually refer patients to specialists, the treatment of prostate cancer will not be discussed in detail here.

As demonstrated in the PIVOT trial, men with low risk or low PSA (<10 ng/mL) have an excellent long-term prognosis with watchful waiting and will represent about 70 % of men diagnosed with prostate cancer [31]. In the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial, biopsy of patients with PSA greater than 3 ng/mL was associated with a reduction in prostate cancer mortality for men aged 55–69 years when compared to the control arm. Nevertheless, it is important to note that PSA is not a dichotomous test, but rather a test that indicates the risk of a harmful cancer over a continuum. In men with a large prostate, older men, and in men with a suspicion of prostatic inflammation, it would be acceptable to withhold biopsy at exceeding 3–4 ng/mL. Unfortunately, evidence to help the family physician decide the best course of therapy based on PSA levels is lacking [32].

8.4.1 Medications/Immunizations and Chemoprophylaxis

Treatment is based on the classification and spread of the tumor. Treatments include watchful waiting; androgen deprivation; retropubic or perineal radical prostatectomy, with or without postoperative radiation therapy to the prostate margins and pelvis; external beam radiation therapy; and brachytherapy (either permanent or temporary radioactive seed implants), with or without external beam radiation therapy to the prostate margins and pelvis.

The PSA level, clinical stage, and biopsy Gleason score are independent predictors of survival without PSA elevation after treatment.

8.4.2 Referrals

Treatment options for prostate cancer are complex and in some cases controversial. Urologic and oncologic referrals are recommended to help guide the family physician.

8.4.3 Counseling and Patient Education

The introduction paragraphs make general recommendations regarding counseling about screening. If the family physician chooses to discuss screening with patients, they should discuss risks and benefits and note that the harms of screening may outweigh any benefit. Benefits of screening include that in the United States, about 233,000 men will receive a diagnosis of prostate cancer, and of those, about 30,000 will die from the disease in 2014 and that about 1 in 100 men may benefit from early diagnosis. Harms include false-positive and negative results and the psychological harm of false-positive test results. Additionally, screening may not improve overall health or increase life expectancy, especially if the cancer has spread at the time of diagnosis. Other harms associated with prostate biopsy include pain, fever, bleeding, infection, and transient urinary difficulties. Harms of treatment include erectile dysfunction, urinary incontinence, bowel dysfunction, and a small risk for premature death. Finally, because at present it is impossible to distinguish tumors that will remain indolent from those destined to be lethal, many men are being subjected to the harms of treatment for prostate cancer that will never become symptomatic.

8.5 Prevention

Epidemiologic studies have suggested that nutritional factors such as reduced fat intake and increased soy protein may have a protective effect against the development of prostate cancer. Vitamins E and C and selenium are not effective at preventing prostate cancer. The use of 5-alpha-reductase inhibitors is under investigation [33].

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8.6 Family and Community Issues

As a final note, there is variability among family physician's approach to screening for prostate cancer. This variability is influenced by personal feelings as well as medicolegal concerns. Patient decision aids may be helpful for the patient and the physician [34]. It is important for family physicians to become familiar with the data and literature on this topic and help patients make the best decisions based on scientific evidence rather than emotional issues that affect both the patient and the physician.

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Surgery of the Male Genital System

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Testicular Torsion

Testicular torsion is a urological emergency requiring prompt recognition and immediate surgical intervention. The age of onset is typically bimodal peaking in neonates and adolescents; [1] however, physicians must maintain a high index of suspicion in all patients who present with acute scrotal pain. Several key clinical features such as the acute onset of pain, vomiting, and an absent cremasteric reflex aid the clinician in identifying patients who need surgical exploration. Timely restoration of blood flow is imperative to avoid ischemic damage and maintain testicular viability. Therefore, surgical referral should never be delayed for imaging studies or manual detorsion. However, manual detorsion may be attempted as a temporizing measure while awaiting surgery and has been shown to be effective.

Testicular torsion occurs when the testis twists on the spermatic cord (Fig. 1). The rotation of the cord leads to ischemia from vascular obstruction and may cause irreversible testicular damage and necrosis. Incidence rates for testicular torsion range between 1/20,000 and 1/25,000 males per year [2, 3]. While torsions can occur at any age, infants younger than 1 year and adolescents between the ages of 12 and 18 are at greatest risk. There are two anatomical types of testicular torsion, extravaginal and intravaginal (Fig. 1). Extravaginal torsion involves the entire testicle to include the tunica vaginalis, but the underlying pathogenesis is unclear [4]. It almost exclusively manifests in the neonatal period with as many as 70 % of cases occurring prenatally [5]. Intravaginal torsion occurs at any age and refers to the twisting of the spermatic cord within the tunica vaginalis. The most common predisposing anatomic variant leading to intravaginal testicular torsion is the "bell-clapper deformity." It occurs in up to 12 % of males [6] and is characterized by the absence of the posterior attachment between the testis and tunica vaginalis allowing for greater mobility as well as the characteristic horizontal lie of the testis. Even so, not all patients with a "bell-clapper deformity" go on to develop testicular torsion.

The differential diagnosis for acute scrotal pain is extensive (Table 1), but several key historical points and exam findings help identify the patients requiring surgical exploration. Testicular torsion classically presents with the sudden onset of unilateral scrotal pain and is frequently associated with nausea and vomiting. Torsion may occur after trauma or during exercise [7], but often patients will awaken at night with pain. Up to 10 % of patients with testicular torsion have an affected first-degree relative [8], and thus a positive family history may further raise suspicion. Exam findings include tenderness, scrotal edema, a high-riding testis, an abnormal horizontal orientation, and an absent ipsilateral cremasteric reflex. Although highly specific for torsion, a horizontal lie of the testicle occurs in fewer than 50 % of cases [9]. The ipsilateral absence of a cremasteric reflex is both sensitive (96 %) and specific (88 %), but case reports exist of testicular torsions with a normal reflex as well [9]. Skin erythema and/or a reactive hydrocele are also possible but are generally considered late findings and correspond with inflammation beyond 12–24 h. Unfortunately, no single finding consistently excludes the diagnosis or proves to be pathognomonic; however, the presence of unilateral pain occurring in last 24 h, associated nausea/vomiting, an absent cremasteric reflex, and a high-riding testis are the most reliable, predictive factors [10]. As a result, several clinical scoring systems have emerged and are undergoing further validation with

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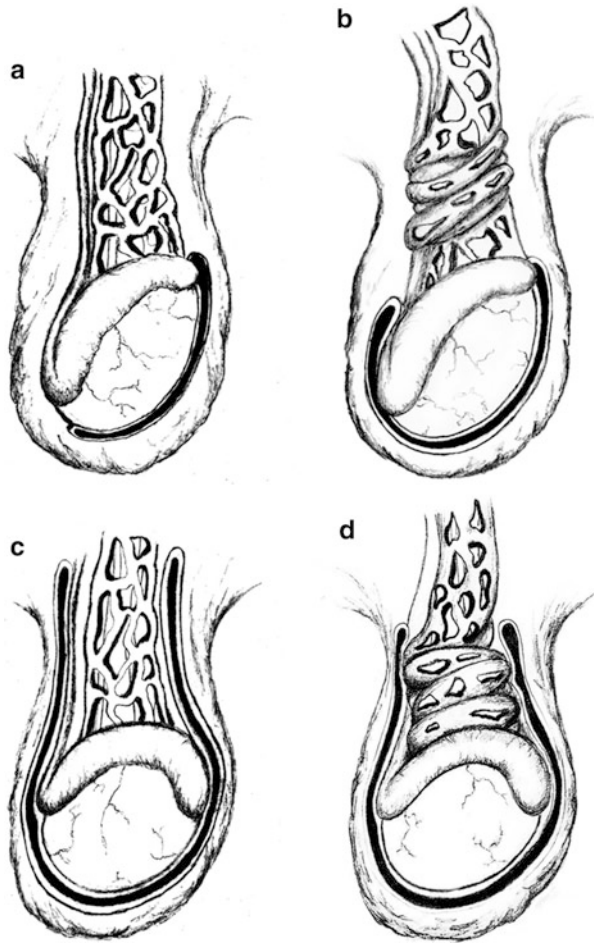

Fig. 1 (**a**) Normal testicular anatomy (*top left*), (**b**) Extravaginal torsion (*top right*), (**c**) Anatomic variant –"Bell-clapper deformity" (*bottom left*) (**d**) Intravaginal torsion (*bottom right*) (Credit: Christine M. Campbell)

promising results that have yielded high sensitivities and lower numbers of unnecessary surgical procedures [10, 11].

When the initial evaluation is consistent with testicular torsion, obtaining additional imaging studies is discouraged to avoid any delay in surgical consultation. However, in cases where the diagnosis remains unclear, color Doppler ultrasonography (CDU) is the test of choice for further evaluation with sensitivity and specificity rates ranging between 89 % and 100 % [12] and a false-negative rate of only 1 % [13]. In the event CDU is not immediately available or the results are inconclusive, the patient should proceed to surgery. Despite the benefits of CDU, time remains the primary drawback, and research is underway to find a point of care test with the accuracy and reliability of CDS. Near-infrared spectroscopy (NIRS) is a technology that uses infrared light to obtain continuous, noninvasive transcutaneous monitoring of deep tissue oxygen saturation [14]. With promising early studies, NIRS has the potential to be a fast, reliable bedside test for testicular torsion in the future [14].

An expeditious urology referral is of primary importance when managing testicular torsion. Irreversible ischemic damage may occur in as little as 6 h, after which testicular salvage rates significantly decline [15]. Preoperative counseling must include the potential need to perform an orchiectomy should the testis be nonviable. The procedure itself involves the intraoperative detorsion and fixation (orchiopexy) of the affected testis via a trans-scrotal approach. In an effort to prevent future torsions, orchiopexy of the contralateral testis is also performed due to the predisposing anatomic defect occurring bilaterally in 80 %

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Table 1 Differential diagnosis of testicular torsion

Infectious:	Epididymo-orchitis Abscess Fournier's gangrene (necrotizing fasciitis) Mumps
Ischemic:	Appendix testes torsion Appendix epididymis torsion
Idiopathic:	Idiopathic scrotal edema Idiopathic testicular infarction
Inflammatory:	Henoch-Schönlein purpura Spermatocele
Traumatic:	Testicular rupture Testicular hematoma Testicular contusion
Structural:	Inguinal hernia Hydrocele Varicocele
Neoplastic:	Testicular cancer Leukemia Lymphoma

Information from Refs. [1, 7]

of patients [16]. Since the restoration of blood flow is paramount, it is reasonable to attempt manual detorsion [17] while awaiting surgical exploration; however, it should never delay or take the place of surgical intervention. Prior to manipulating the scrotum, ensure the patient has adequate analgesia with intravenous medications, a spermatic cord block, or both. Rotation of the testis is typically performed in a medial to lateral direction (toward the patient's thigh) as if opening a book since the testis often rotates medially with a torsion, yet physicians should keep in mind that a lateral rotation may be present in up to one third of cases [18]. Multiple rotations may be necessary as the testis can be twisted as much as 720°. Indicators of a successful detorsion include the improvement of pain, a lowered position of the testis within the scrotum, reorientation of the testis to a longitudinal lie, and the return of blood flow on CDU. Even in the event of a successful manual detorsion, surgical exploration and orchiopexy are required to reduce the chance of recurrence.

A potential pitfall that physicians must keep in mind is the possibility of intermittent torsion. The diagnosis is often elusive since the pain may be resolved by the time the patient presents for evaluation. A history of spontaneously resolving episodes of acute scrotal pain separated by lengthy periods of time [19] should raise suspicion and is often the only indicator of intermittent torsion. A bulky spermatic cord, mobile testes, and a horizontal lie are possible, but a normal exam doesn't exclude the diagnosis. Nausea and vomiting occur much less frequently, and CDU is only about 75 % sensitive. Therefore, it is imperative that clinicians maintain a high index of suspicion for intermittent torsion and ensure urological follow-up is expedited.

Neonatal Circumcision

Male circumcision is an elective procedure most frequently performed in the neonatal period that involves the surgical removal of the prepuce (i.e., foreskin) for medical, religious, or cultural reasons. Much debate has surrounded the risks versus benefits of this procedure; however, a growing body of evidence has

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emerged that outlines several medical benefits of circumcision. Although rare, complications such as bleeding, infection, or scarring can occur, and physicians must be able to recognize and manage these accordingly. Physicians should provide nonbiased, factual information to parents about the procedure while remaining sensitive to cultural or religious factors when seeking informed consent. The three primary techniques for neonatal circumcision include the Gomco clamp, Hollister Plastibell®, and Mogen clamp.

Male circumcision is one of the oldest and most common surgical procedures with an estimated global prevalence of 30 % [20]. In the United States (U.S.A.), up to 81 % of males are circumcised, but notable differences exist among ethnic groups (91 % of whites, 76 % of blacks, 44 % of Mexican Americans) [21]. When looking at the reasons behind parental decision-making, 30–40 % of parents cited social influence or religious preference, but medical benefits and hygiene were the most common reasons for circumcision and were reported in as many as 67 % of respondents [22].

Opponents of neonatal circumcision voice concerns over procedural risks, pain, psychological trauma, potential decreased sensation, and the infant's inability to give consent. However, decreased sensation or psychological trauma from circumcision have not been supported in the literature [22, 23]. Furthermore, parents are legally authorized to provide consent for medical procedures that are in the best interest of their children, thus any discussion regarding the ethical nature of parental consent would necessarily include all procedures, not just circumcision. Therefore, it is the physician's responsibility to correct common misconceptions and ensure accurate information is communicated to families regarding the potential sequelae of neonatal circumcision. Historically, professional societies have been reluctant to advocate for or against circumcision due to the lack of quality studies and conflicting outcomes. However, recently the American Academy of Pediatrics (AAP) released a policy statement endorsed by the American College of Obstetrics and Gynecologists (ACOG) stating that evidence now suggests the preventive health benefits of circumcision outweigh the risks. Although they do not recommend routine circumcision for all newborns, the task force concluded that the benefits justify access to the procedure for families who choose it [24]. Similarly, the American Urological Association's (AUA) statement highlights the potential benefits of neonatal circumcision and affirms that the incidence of serious complications is extremely low [25]. Both statements emphasize the importance of communicating risks and benefits to parents accurately and without bias.

Potential health benefits of neonatal circumcision include a decrease in urinary tract infections (UTI), penile retractile disorders, penile cancer, and several sexually transmitted infections (STI). Protection against UTIs is greatest in the first year of life with a 90 % reduction; however, additional benefits are also conferred since the lifetime risk of UTI in males is similarly reduced, dropping to 9 % from 32 % in uncircumcised men [26]. Phimosis and paraphimosis are effectively eliminated with circumcision, and balanoposthitis has been shown to occur less frequently in circumcised males. Strong evidence supports the protective effects against penile cancer, but the clinical significance is unclear considering the overall low incidence. A reduction in the acquisition and transmission of human papillomavirus (HPV), herpes simplex virus type 2 (HSV-2), and *Trichomonas vaginalis* has been demonstrated in several studies [27]. Furthermore, a Cochrane review of studies in Africa affirmed the preventive effect of circumcision in heterosexually acquired human immunodeficiency virus (HIV) [28]. In fact, the World Health Organization (WHO) even recommends considering circumcision as part of a comprehensive approach to HIV prevention [29]. When examined collectively by a Mayo Clinic risk-benefit analysis, the benefits of neonatal circumcision over a lifetime exceeded the risks by 100 to 1 [27].

Despite these potential benefits, as with any procedure, risks still exist. Overall, adverse events associated with neonatal circumcision are estimated at <0.5 % in the USA [30] and 1.5 % worldwide [31]. The rate of serious adverse events is even lower at 1 in 5,000 circumcisions [27]. Bleeding is the most common complication and typically occurs along the incised skin edges or due to frenular artery

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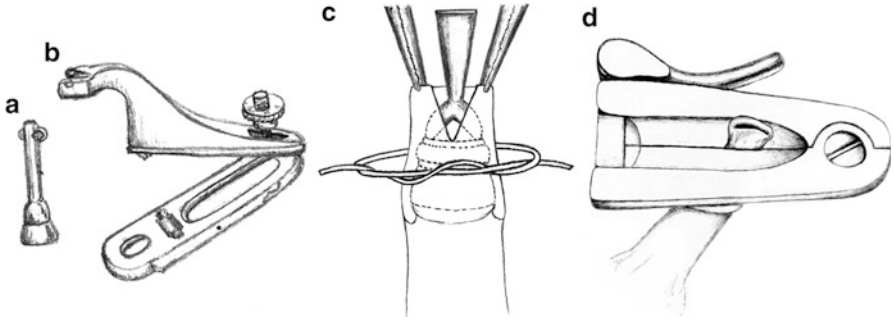

Fig. 2 (**a**) Gomco Clamp (*left*) (**b**) Hollister Plastibell® (*center*) (**c**) Mogen Clamp (*right*) (Credit: Christine M. Campbell)

disruption. The majority of bleeding can be stopped with manual pressure although severe bleeding is possible, especially in the setting of an underlying coagulopathy. If a family history or clinical suspicion of a bleeding disorder exists, consider postponing the procedure until labs can be obtained to rule out a bleeding diathesis. When manual pressure is insufficient to control bleeding, the physician may attempt topical application of lidocaine with epinephrine (1:100,000), silver nitrate, or consider using fine absorbable suture for hemostasis [32]. Another potential complication is a localized wound infection. Most cases are managed with topical antibiotics and close follow-up, but rarely, a severe infection will require systemic antibiotics. In approximately 1 per 1,000 circumcisions [27], a second surgery may be necessary. Reasons for this include excessive/inadequate skin removal, glans injuries, meatal stenosis, urethrocutaneous fistula, epidermal inclusion cysts, and scarring (adhesions, skin bridges, or cicatrix formation). Pediatric urology consultation is recommended for any complications requiring revision.

Neonatal circumcision is typically performed between the first and eighth day of life. Bleeding diathesis, congenital defects (hypospadias, congenital buried penis, etc.), prematurity, and clinical instability are all contraindications. After counseling the family on the risks and benefits, a signed consent should be obtained and a timeout performed prior to the procedure. Physicians must ensure all necessary instruments and supplies are present, sterile, and inspected for defects. Analgesia should be used for all circumcisions and can be provided in various ways. Topical anesthetics such as eutectic mixture of local anesthetics (EMLA) cream are reasonable options but are less effective than infiltrative anesthesia [33]. Oral sucrose is also effective for pain control [34] with some evidence suggesting additional benefit when combined with an anesthetic [35]. A dorsal penile nerve block is performed by infiltrating 0.5 mL of 1 % lidocaine at the 10 and 2 o'clock positions near the base of the penis. The needle should be directed slightly medially as the dorsal penile nerves sit at 1 and 11 o'clock [36]. Another effective infiltrative technique is the ring block. This is accomplished by starting laterally at the base of the penis and subcutaneously injecting 0.5 mL of 1 % lidocaine 180° around the base of the penis. The needle is removed and the process is repeated on the contralateral side so as to form a complete "ring" around the penis [36]. With both infiltrative techniques, ensure aspiration is performed prior to injection and adequate time is given for the anesthetic to take effect.

There are three primary techniques physicians use to perform neonatal circumcision: the Gomco clamp, the Hollister Plastibell®, and the Mogen clamp. All three techniques require the physician to take down adhesions between the glans and the prepuce with blunt dissection prior to removing the foreskin. Care must be taken not to injure the frenulum at the ventral 6 o'clock position. The Gomco clamp is a metal device designed to circumferentially clamp the prepuce during circumcision (Fig. 2). The bell of the device is designed to fit under the prepuce and over the glans, protecting it from injury. Inspecting the device for flaws and ensuring the bell size matches the base plate are necessary safety measures. When used properly, the Gomco clamp reduces the risk of injury to the glans penis and shaft, although the procedure itself may be slightly more time consuming than other techniques as the clamp should be left in

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place at least 3–5 min. The Hollister Plastibell® (Fig. 2) is a plastic device with a grooved bell-shaped ring that is placed under the prepuce and over the glans similar to the Gomco clamp. Once in place, a suture is tied around the prepuce and rests in the groove of the bell, restricting blood flow. The plastic handle is then snapped off leaving the device in place until the prepuce necroses and falls off (usually 6–12 days). Since no incisions are made, bleeding complications are rare. However, if placed improperly or if the plastic ring slips onto the penile shaft, serious complications such as damage to the urethra, glands, or shaft can occur. The Mogen clamp (Fig. 2) is much different from the other techniques. After adhesions to the glans have been taken down, the prepuce is drawn up above the glans, and the Mogen clamp is slid over the prepuce just distal to the glans at the angle of the corona. Prior to closing the clamp, the glans should be manipulated side to side to ensure only skin is in the clamp. Once closed, the prepuce is cut and the clamp removed. The remaining skin is then retracted, exposing the glans. When performed properly, this technique removes more skin dorsally than ventrally. Circumcisions can be performed more quickly using the Mogen clamp, but the glans is not well protected allowing for possible injury. Physicians should undergo specific training and supervision prior to attempting any of these techniques in order to reduce the risk of complications.

Vasectomy

Vasectomy is the most reliable and cost-effective form of long-term contraception for men. It is a safe, permanent procedure performed in the outpatient setting and is highly effective. Complications include bleeding, infection, sperm granuloma, and postvasectomy pain syndrome, but an experienced surgeon can reduce the risk of adverse events. The no-scalpel technique is superior to traditional incisional approaches due to lower complication rates and improved recovery times. A successful procedure may be confirmed by a single semen analysis at least 3 months post vasectomy.

Family medicine physicians perform approximately 13 % of the >500,000 vasectomies done in the U.S.A. each year [37]. Reimbursement for vasectomy averages between $300–$900, which is comparable to or below the costs for long-term female contraceptive options. In contrast to female sterilization, vasectomy is performed in an office setting and avoids the use of general anesthesia making it more cost effective and safer than tubal ligation. The overall failure rate for vasectomy is reported to be <1 % [38]. It is important that patients understand vasectomy is meant to be a permanent form of birth control. While vasectomy reversal is possible, the cost of the procedure is high, and success rates vary [38]. Candidates least likely to seek reversal after a vasectomy are men over 30 in stable, committed relationships [38].

Despite the relative safety and efficacy of the procedure, operative experience significantly impacts complication rates. Physicians who perform less than 10 procedures per year have three times the complications than those performing more than 50 [39]. Bleeding is the most common complication and can lead to hematoma formation. Using the no-scalpel technique, hematoma risk is reduced to 1–2 % from as much as 10 % with incisional methods [40]. The majority of hematomas are managed conservatively with scrotal support, warm baths, and analgesics; however, rare cases may require scrotal exploration or hematoma evacuation. Postoperative infection is another possible complication. As with bleeding, infection risk is reduced by using the no-scalpel technique and occurs in <1 % of cases [40]. Oral antibiotics that cover common skin flora are the first-line treatment for postoperative infections.

Sperm granulomas and postvasectomy pain syndrome are chronic conditions that can arise after vasectomy. A sperm granuloma presents as a painless scrotal mass weeks to months after the procedure and is caused by an immunologic reaction to sperm that leaks from the testicular vas opening. Patients can be reassured that most granulomas resolve spontaneously over time and are generally considered

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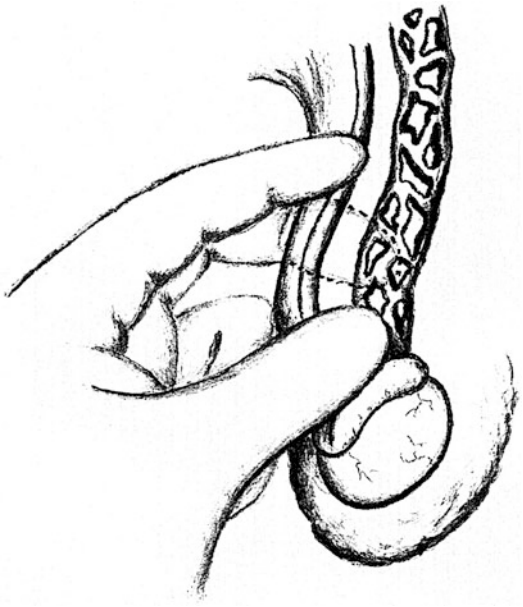

Fig. 3 Isolation of the vas deferens using the three finger technique (Credit: Christine M. Campbell)

protective against epididymal congestion; [41] however, they may also play a potential role in postvasectomy pain syndrome or recanalization leading to vasectomy failure [42]. Postvasectomy pain syndrome refers to varying degrees of chronic pain that persist months to years after a vasectomy secondary to chronic congestive epididymitis [38]. Incidence rates vary in the literature, but according to the AUA, 1–2 % of men experience chronic pain that negatively impacts their quality of life [43]. Management is primarily conservative, but nerve blocks or steroid injections may be considered. Occasionally, refractory cases require additional surgery such as vasovasostomy (vasectomy reversal) or epididymal resection.

Several other medical conditions have been studied for any correlation to vasectomy [44]. No associated increased risks for cardiovascular disease, testicular cancer, or autoimmune disease have been identified. However, a twofold risk for nephrolithiasis was observed in men younger than 46, but the physiological mechanism remains unknown. Any associated risk with prostate cancer remains controversial. Although one study indicated a small increased risk for advanced prostate cancer after vasectomy [45], the AUA guidelines do not recommend routinely counseling patients on a causal relationship between vasectomy and prostate cancer [43].

Preoperatively, a complete urological exam should be performed to ensure the patient has accessible and mobile vas deferens bilaterally without evidence of anatomic abnormalities such as varicoceles, hydroceles, masses, or cryptorchidism. Contraindications for the procedure include local infection, bleeding diathesis, and abnormal findings on exam. Often, physicians may choose to provide an anxiolytic and/or pain medications to be taken orally 45–60 min before the procedure to help relax the patient. Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided for 5–7 days prior to the procedure to reduce the risk for bleeding.

The procedure is performed with the patient in the supine position allowing the penis to be draped or taped to the lower abdomen for unobstructed access to the scrotum. The area is prepped with an antiseptic solution and draped using sterile technique. Isolation of the vas deferens is typically performed by using a three-finger technique (Fig. 3) with the nondominate hand. Anesthetic (1 % lidocaine without epinephrine) is infiltrated at the incision site creating a small wheal. A nerve block is then accomplished by fully inserting the needle along the vas sheath toward the inguinal ring and after aspiration injecting 2–5 mL of

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anesthetic into the surrounding tissue as the needle is withdrawn [46]. An emerging alternative to infiltrative anesthesia is the use of a high-pressure jet injector to deliver the anesthesic through intact skin. This does not require a needle and reduces the pain from anesthetic administration; however, the widespread use of this technique is limited by the initial cost of the device.

Accessing the vas deferens should be accomplished by using the no-scalpel technique. Originally developed in China, it is now the preferred technique in the U.S.A. because it reduces procedural time as well as recovery time and has been shown to decrease the risk of bleeding, hematoma, infection, and pain [40]. In contrast to a more traditional incisional approach, the no-scalpel technique utilizes a smooth, sharp-tipped, curved hemostat to puncture a hole in the skin and spread the tissue. The vas deferens is then elevated through the skin with a vas clamp, and the perivasal tissue is dissected or incised, further exposing the vas. The exposed vas can be regrasped with a second vas clamp or towel clip which further elevates the vas out of the skin. The residual tissue and associated blood vessels can then be carefully removed either with blunt dissection or instrumentation to fully isolate 1–2 cm of the vas. The vas is subsequently divided, and although there is no minimum length of vas recommended for removal [43], many physicians will excise 1–1.5 cm.

There are multiple ways to manage the vasal ends including fulguration, ligation, clips, and interfascial positioning. Fulguration (intraluminal cautery or electrocautery) may be used to occlude both ends or just the prostatic end of the vas. Leaving the testicular end open theoretically reduces epididymal congestion but may predispose the formation of a sperm granuloma. Ligation should be avoided due to its higher failure rates [47]. The evidence for the use of clips is underpowered and low quality, while interfascial positioning has been proven to reduce vasectomy failures [48]. Interfascial positioning is performed by using an absorbable suture or clip to separate the vasal ends with the vas sheath. A combination of fulguration and interfascial positioning has been shown to be highly effective [47, 48]. After addressing the vas ends, inspection of the area should confirm hemostasis. The vas can then be gently tucked back into the scrotum by lifting the scrotal skin on each side of the opening. Skin closure is not necessary when using the no-scalpel technique. Physicians may choose to make a second entry point for the contralateral side, or if the original opening was near the midline, the opposite vas can be brought through the same hole.

Postoperative care instructions should be provided to the patient. Having the patient bring a supportive undergarment is beneficial for patient comfort after the procedure. Encourage rest from activity and intermittent application of ice to the scrotum for 48–72 h. Analgesia with acetaminophen or NSAIDs is often sufficient, and pain requiring stronger medications beyond 48–72 h should be evaluated. It is reasonable for patients to resume light activity or work within 2–3 days, but exercise, sexual activity, or lifting should be avoided for 1 week. Remind the patient that an alternate form of contraception is required until infertility is confirmed by postvasectomy semen analysis (PVSA). A single specimen is sufficient as long as 20 ejaculations have occurred and at least 3 months since the procedure have passed [49]. If motile sperm are seen, consider repeating the PVSA in 1–2 months. Vasectomy failure is defined as the presence of motile sperm on PVSA 6 months after the procedure [43].

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Family Medicine
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Selected Disorders of the Genitourinary System

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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 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

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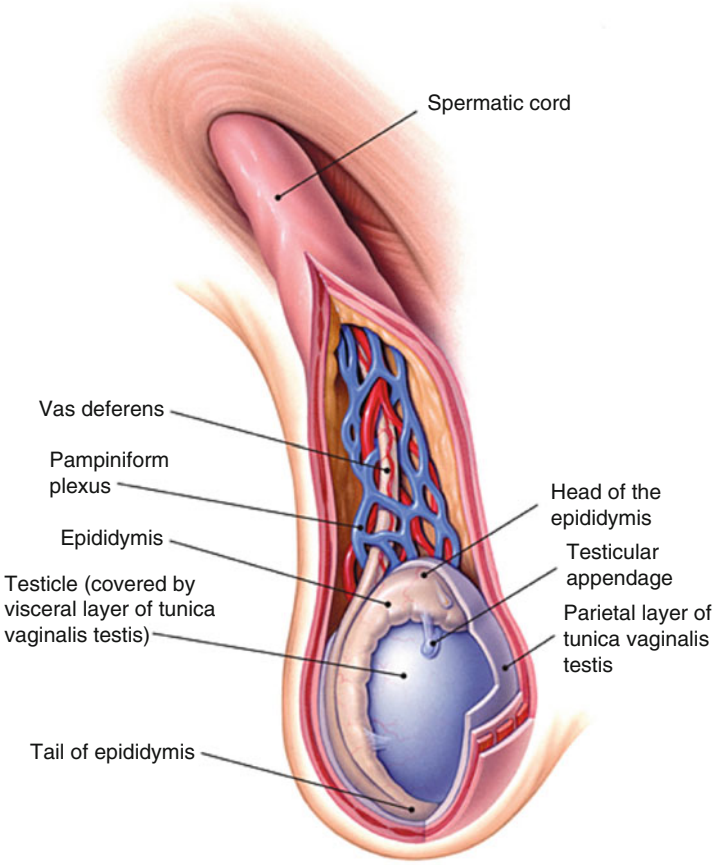

Fig. 1 Anatomy of scrotal contents

conflicting evidence about the association between varicoceles and male infertility [1]. A Cochrane review of ten randomized trials found some increase in fertility from surgical treatment of varicoceles in couples with unexplained subfertility (number needed to treat = 17) [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 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*

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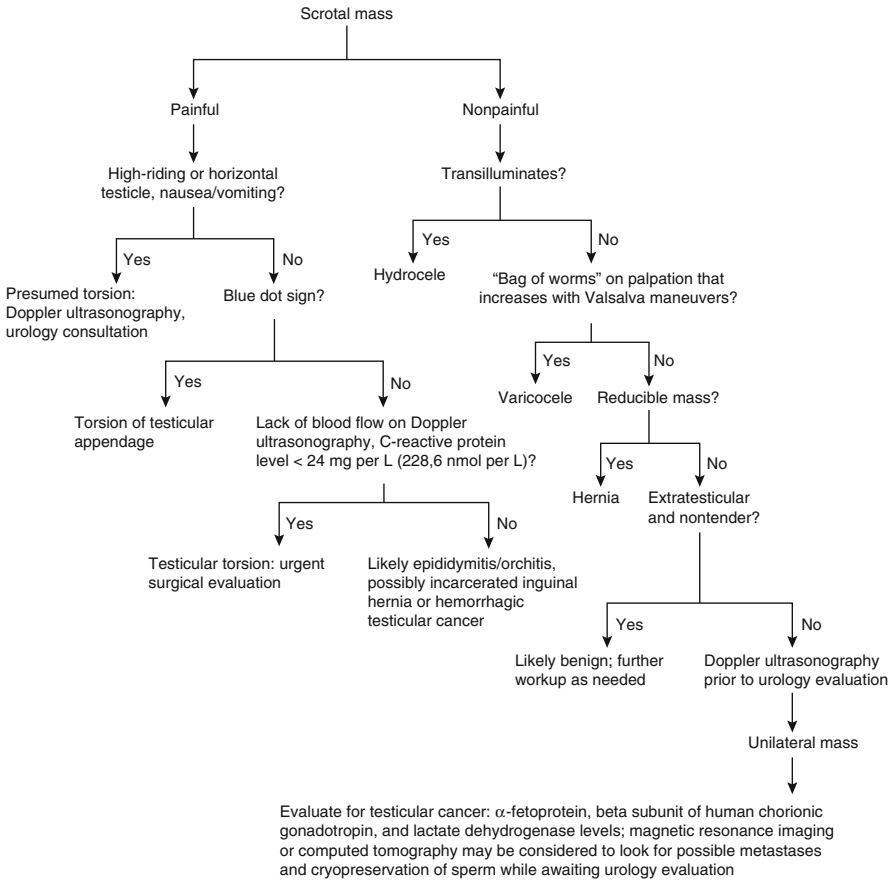

Fig. 2 Algorithm for evaluation of a scrotal mass

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, ciprofloxacin (Cipro) 500 mg orally twice daily for 10–14 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 chapter 106.

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

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bacteria 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 4 out of 100,000 men, testicular cancer is the most common solid tumor among men between the ages of 20 and 34 years old [8]. 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 14-fold. Early orchidopexy (before 1 year of 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, and white race [9].

Screening The US Preventive Services Task Force does not recommend screening for testicular cancer with either self- or physician examination [10].

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 new evidence that testicular sparing surgery may be satisfactory in selected patients [11]. 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.

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Treatment

Clinical stage and histology determine appropriate therapy. Typical chemotherapy agents include bleomycin (Blenoxane), etoposide (Vepesid), and cisplatin (Platinol AQ).

Seminoma [8, 9]

- Stage I is generally treated with radiation; however, observation and limited chemotherapy are options.
- Stage IIA is treated with radiation to the regional lymph nodes.
- Stage IIB or IIC is treated with three cycles of three-drug chemotherapy.
- Stage III is treated with three-drug chemotherapy; but if there is no response, consider clinical trials of other chemotherapy drug combinations, and if brain metastasis is present, treat with radiation of the brain or surgical removal.

Nonseminoma [8, 9]

- Stage I is treated with retroperitoneal lymph node dissection or observation with monthly follow-up.
  - Stage IB is generally treated with two cycles of chemotherapy.
  - Stage IS patients are treated with full-dose chemotherapy if serum tumor marker levels do not rapidly fall.
  - Stage IIA patients are treated with retroperitoneal lymph node dissection followed by observation with monthly follow-up and frequent laboratory testing OR two cycles of two-drug chemotherapy.
  - Stage IIB or IIC patients receive three or four cycles of three-drug chemotherapy followed by retroperitoneal lymph node dissection if computed tomography still shows lymph nodes. If high-serum tumor marker levels are present, chemotherapy is followed by lymph node dissection.
  - Stage III patients should have three-drug chemotherapy and surgical removal of persistent tumors. Patients with high-serum tumor marker levels often do not respond to usual chemotherapy.

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. About 50,000 men and 17,000 women are diagnosed with this disease while 14,000 die from it annually. The incidence of bladder cancer increases with age in men and women. Eighty percent of cases occur in those over 60 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. Aromatic amine occupational exposures account for 5–10 % of bladder cancer cases in industrialized nations. Chronic infection with *Schistosoma haematobium*, genitourinary tuberculosis, or chronic urinary tract infection are risk factors [12]. Patients treated with cyclophosphamide (Cytoxan) have up to a ninefold increased risk that occurs 6–13 years after the exposure, but administration of 2-mercaptoethanesulfonic

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acid (Mesna) can reduce the carcinogenic properties of cyclophosphamide. Pelvic irradiation can also increase bladder cancer risk.

Pathology

About 90 % of bladder cancers diagnosed in the U.S.A. are urothelial, formerly known as transitional cell, carcinomas.

Squamous cell carcinoma accounts for about 7 % of bladder cancers in the U.S.A. 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].

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].

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 specificity (95–100 %) but a low sensitivity (66–79 %) for the detection of bladder cancer. Tumor markers are not useful [12].

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 3 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 perivesicle 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

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mitomycin. T2a through T3b are treated with radical cystectomy 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 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 U.S.A. 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 U.S.A., 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].

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, are the next most common metabolic abnormalities 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.

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Table 1 Causes of urolithiasis [15–18]

Obesity
Diabetes
Hypercalciuria
Idiopathic (absorptive types I and II)
Renal
Unclassified
Primary hyperparathyroidism
Hyperuricosuria
Cystinuria
Gouty crystal deposits
Stones secondary to urinary infection
Renal tubular acidosis type 1
Hypocitraturia
Hypomagnesuria
Hyperoxaluria
Increased dietary fructose intake
Medications and supplements
Allopurinol
Antibiotics (Sulfonamides, ampicillin, amoxicillin, ceftriaxone (Rocephin), quinolones, furans, pyridines)
Carbonic anhydrase inhibitors (Acetazolamide, topiramate (Topamax)
Ephedra alkaloids
HAART (highly active antiretroviral therapy)
Laxatives
Potassium channel blockers (amiodarone, sotalol)
Potassium-sparing diuretics (triamterene)
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 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. Using Hounsfield density helical CT allows one to differentiate uric acid, cystine, and calcium containing stones from one another and to subtype calcium stones.

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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, hydronephrosis, concomitant pregnancy, and renal failure. Those patients with refractory pain 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 L a day is essential. 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 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 antiinflammatory 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, 19]. 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.

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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

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

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. 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 concomitant increase in fluid intake to maintain a urine volume of >2 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.

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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

Nondietary 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.

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 or 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, are recommended.

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 potential adverse effects [15].

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Family Planning and Contraception

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Unintended Pregnancy

Ever since 1980, reducing unintended pregnancy has been a key goal of the Healthy People national health initiative. The unintended pregnancy rate in the United States (US) still remains one of the highest in the developed world. According to the latest National Survey of Family Growth (NSFG) study from 2010, nearly 49 % of the 6.7 million pregnancies in the USA were unintended in 2006 consistent with 52 unintended pregnancies for every 1,000 women aged 15–44 [1]. The outcome of these pregnancies has been remarkably stable over time, with 40 % eventuating in abortion as recently as 2008 [2]. Evidence in the literature suggests that unintended pregnancy poses both immediate and long-term adverse health risks for baby and mother, such as delayed prenatal care, poorer health in childhood, lower breastfeeding rates, and increased exposure to cigarette smoke [3]. Children born from unintended pregnancies are more likely to live in poverty, less likely to graduate high school and experience more behavioral problems in their teen years. These adverse outcomes are significantly amplified in the case of teen mothers, resulting in an average annual cost to US taxpayers from teen parenting estimated at $9.4 billion USD in 2010 [4].

Tools to Help You (and Your) Patient Choose

Contraceptive decisions are a risk analysis that involves assessing the risk of pregnancy, assessing the risk of the contraceptive method, and assessing the probability that the patient will be able to tolerate and use the method effectively. Contraceptive decision making also involves assessing the risk that a method might worsen a medical problem, the risk that the method won't work at all, the risk that the patient won't use the method effectively, and the risk that the patient won't use abortion as a last backup in the event of method failure.

There are well-documented non-contraceptive health benefits to many contraceptives, whose characteristics also play a part in the contraceptive choice process. Such benefits as lower lifetime risk of uterine and ovarian cancer for users of combined hormonal contraceptives (CHCs) or the decreased menstrual flow characteristic of the levonorgestrel intrauterine system (LNG-IUS) need consideration in the process of selecting the optimal method.

The World Health Organization (WHO) published its Medical Eligibility Criteria for Contraceptive Use (MEC) in 1996, perhaps the first publication giving evidence-based guidance on the safety of contraceptive method use for women and men with certain characteristics and medical problems. The United States Centers for Disease Control (CDC) adapted the WHO MEC for use in the United States, reflecting US practice patterns and removing reference(s) to methods that may not be available in the USA. The US MEC was developed with the specific intent to provide evidence-based guidance regarding family planning practices, to address misconceptions surrounding the safe use of contraceptive methods, to reduce medical barriers to safe contraception, and lastly to improve access and quality of care in family

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planning. It is accessible at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5904a1.htm?s_cid=rr5904a1_e [5], and applications for smart phones and computer tablets are available as downloads as well. Central to the US MEC is a categorization of contraceptive methods based on medical conditions that may have an impact on the ability of a patient to utilize a particular contraceptive method.

The matrices in the US MEC include evidence-based recommendations for the use of contraceptive methods by women and men with particular characteristics and/or medical conditions; it is by no means an exhaustive list. Each condition was defined as either representing an individual's characteristics (e.g., age, history of pregnancy) or a known preexisting medical/pathologic condition (e.g., diabetes or hypertension). Recommendations may be different depending on whether or not a particular method is being initiated or merely continued. The primary focus of the US MEC recommendations is the safety of a given contraceptive method for women with medical conditions or characteristics; the categories listed in Table 1 generally do not take method effectiveness into account, so while a method in Category 1 can be used without restriction as regards safety, that method may be not be optimal for a patient's particular medical condition.

A companion document, the US Selected Practice Recommendations for Contraceptive Use (US SPR), was published in 2013 and represents an adaptation of the WHO SPR for providing guidance to health-care professionals when they counsel patients about contraceptive use [6]. The CDC intends its use to be an evidence-based guidance for common, sometimes controversial contraceptive management questions. The US SPR is slightly different from the WHO document in that, once again, adaptations are made accounting for differences in available contraceptive methods, some of the recommendations for testing prior to contraceptive method initiation and some simplified "missed pill" algorithms. It can be found at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6205a1.htm?s_cid=rr6205a1_w [7]. Both CDC resources are continuously updated to reflect new data as it becomes available, ensuring that they are based on currently available evidence.

Taken together, the US MEC and SPR are powerful resources to help dispel the many myths surrounding contraceptive use which can serve as barriers to effective contraceptive use and thus improve patients' contraceptive experience by avoiding unintended pregnancies.

Health-care providers should provide patients with the most effective contraceptive method(s) that fit their particular clinical situation. Toward this end, not only are the risks and benefits of a particular contraceptive method balanced but also the risk(s) that an unintended pregnancy might pose. For example, it may not be the best practice to recommend a barrier method of contraception to a woman with congenital heart disease such as Eisenmenger syndrome; such a patient should avoid pregnancy at all costs given the attendant 20–60 % maternal mortality of delivery at term. Physicians must continually be aware of the contraceptive needs of patients, remembering that women with medical problems have sex and do get pregnant.

Table 1 Categories of medical eligibility criteria for contraceptive use

1	No restriction for the use of the contraceptive method for a woman with that condition
2	Advantages of using the method generally outweigh the theoretical or proven risks
3	Theoretical of proven risks of the method usually outweigh the advantages – not usually recommended unless more appropriate methods are not available or acceptable
4	Unacceptable health risk if the contraceptive method is used by a woman with that condition

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Patient Education and Activation

Providing timely, understandable, and clear education regarding the contraceptive method chosen is an essential component to enhance effectiveness. Patient education is fundamental to any patient's ability to make an informed decision regarding contraceptive choice and adherence. There are many resources available for patient self-education on contraceptives. These include office handouts like the one available from the CDC shown in Fig. 1. Web-based resources for patients from the CDC, Planned Parenthood, ACOG, and the Association of Reproductive Health Professionals are also available including interactive tools and videos to help patients decide which contraceptive is right for them.

Contraceptive Effectiveness

The focus of contraceptive choice has changed dramatically over the past few years. Whereas once providers began the process of contraceptive counseling with combination hormonal contraceptives (CHCs) such as pills, patch, and ring, it has become clear that relying on theoretical effectiveness estimates of particular methods may not be in the best interests of patients. While CHCs may have theoretical effectiveness of >99 %, in actual use, failures approach 6–12 pregnancies per 100 woman-years. Inconstant adherence to a strict user-dependent regimen, the cost of many CHCs, and varying insurance coverage for contraceptive methods all combine to make theoretical effectiveness nearly unreachable. In the following figure from the CDC, methods are arranged in tiers from most to least effective. It should be apparent from the table that user-independent methods (intrauterine devices, implants, and permanent contraception) have the lowest failure rates, approaching <1 pregnancy per 100 woman-years.

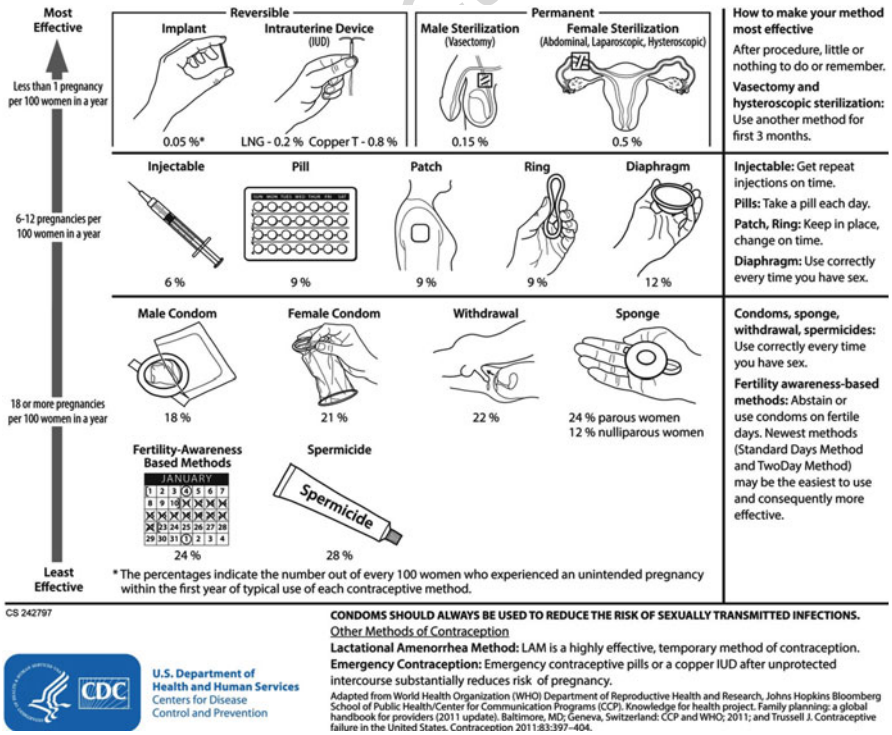

Fig. 1 Effectiveness of family planning methods

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Long-Acting Reversible Contraception and the Contraceptive CHOICE Project

An innovative clinical study attempted to determine the impact on the usage of long-acting reversible contraception (LARC) by removing financial and knowledge barriers to access of contraceptive methods including CHCs and LARC (IUDs, implants, and injectable contraceptives) [8]. The results of the study indicated a remarkable 67 % of women who enrolled chose LARC methods (56 % chose intrauterine contraception and 11 % chose the subdermal implant). The same held true for the adolescent population within the study group in which 69 % of 14–17 year olds chose LARC, demonstrating that appropriately counseled teens accept LARC in large numbers [9]. The CHOICE Project demonstrated a clear reduction in the rate of unintended pregnancy in adult and adolescent women and the highest rates of contraceptive continuation out to 24 months of study [10]. Concomitantly the abortion rate for members of the CHOICE cohort was less than half the regional and national rates, and the repeat abortion rates declined significantly as well [11]. As a result of the findings of this ongoing study, national organizations including the American Congress of Obstetricians and Gynecologists (ACOG), the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP) have all issued practice bulletins, practice guidelines, and technical reports endorsing the utilization of LARC methods as a means to reduce unintended and teen pregnancy rates [12–14]. The focus of these organizations underscores the need to redirect and emphasize patient counseling efforts toward a "LARC-first" approach to contraception.

Intrauterine Devices and Systems (IUDs and IUS)

Modern IUDs are the most popular means of contraception in the world outside of the USA, with an estimated 100,000,000 users in China alone based on a contraceptive prevalence of 53 % of contracepting women aged 15–44. In the USA, however, IUD popularity and use have waxed and waned at much lower rates, due in large part to economic forces brought about by periodic intense adverse litigation, despite its track record of safety and efficacy.

It has been known for many years that the main mechanism of action of modern IUDs is that of a spermicide [15]. With respect to copper containing IUDs, the copper ion itself has been found to be toxic to human spermatozoa and to human ova; it also enhances inflammatory responses which are toxic to spermatocytes and oocytes. Midcycle tubal washout studies in women wearing copper IUDs demonstrated that no fertilized ova were retrieved from IUD users [16]. These effects occur prior to fertilization; no documented postfertilization effect has been established. The mechanism of action for levonorgestrel-containing IUDs (Mirena®) is strikingly similar to that of copper containing ones. Since levonorgestrel (LNG) is a potent progestin, it exerts a powerful effect on human cervical mucus, thickening it significantly so that it acts as a spermicidal barrier. It directly inhibits sperm capacitation without which fertilization cannot occur while simultaneously causing atrophy of the endometrium, reducing its ability to aid in sperm ascent into the upper genital tract. The atrophic endometrium thus produced is likely also responsible for the dramatic reduction of menstrual flow seen in users of the LNG-IUD.

Currently, there are three IUDs marketed in the USA: the T380A (Paragard®) and two levonorgestrel-releasing IUDs (Mirena® and Skyla®). The latter two are sometimes referred to as intrauterine systems (IUS) as opposed to intrauterine devices. All these IUDs are T-shaped polyethylene devices that conform to the shape of the uterine cavity and are impregnated with barium sulfate such that they are radiopaque. The arms and stem of the Paragard® contain 380 mm^2 area of exposed copper and is approved for 10 years continuous use. Patients with a history of Wilson's disease or known allergy to copper are not candidates to use Paragard®. The LNG-IUS Mirena® and Skyla® contain 52 mg and 13.5 mg levonorgestrel,

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respectively, in a steroid reservoir. Skyla® is smaller than Mirena® and has advantages for use in nulliparous women; it is approved for use for 3 years, whereas Mirena® is approved for 5 years continuous use. All three IUDs have monofilament threads attached at the base to facilitate removal.

The US MEC lists the following as contraindication to IUD use: 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 [17].

A number of myths and misconceptions surrounding IUDs have served as barriers to wider acceptance by providers and hence are barriers to use of these methods by patients. There is no scientific evidence for a postfertilization mechanism of action of IUDs. For many years, providers were unwilling to employ IUDs in patients with a history of or risk factors for pelvic inflammatory disease (PID). However, the risk of developing pelvic infection is increased only in the first 20 days after IUD insertion, implying that bacterial contamination associated with insertion is the cause of infection, not the IUD itself. A review of the WHO IUD clinical trial data of nearly 23,000 IUD insertions and over 51,000 woman-years of follow-up showed the overall PID rate to be quite low and constant after the first 20 days post-insertion [18]. A troublesome barrier to increased IUD usage in the USA is the frequent mandate that women desirous of IUD insertion be first tested for and known to be free of such STDs as chlamydia and gonorrhea. The delay waiting for the testing results is an unnecessary obstacle; there is ample evidence in the literature for same-day screening for STDs and IUD placement, especially in asymptomatic low-risk women [19]. Routine use of prophylactic antibiotics at the time of insertion is not required. Current algorithms for treating mild to moderate pelvic inflammatory disease in women with an IUD in situ do not call for IUD removal, unless there is no significant clinical improvement with standard antibiotic regimens in 72 h [20].

Another myth associated with IUD use is that of infertility, especially in nulligravid women. A case-control study conducted of nearly 2000 infertile women identified exposure to chlamydia associated with infertility; neither tubal infertility nor duration of IUD use was associated with infertility. IUDs have been associated with the development of ectopic pregnancy (EP), due in part to conflicting findings among some published studies. However, a meta-analysis of published literature from 1977 to 1994 showed that the odds ratio (OR) of EP in IUD users was 1.06 (95 % CI: 0.91–1.24) [21]. This data confirms that IUDs are incredibly efficient at preventing pregnancy overall; however, when a pregnancy occurs with an IUD in situ, the pregnancy may be more likely to be ectopic. Most certainly, a woman with an IUD in situ and a positive pregnancy test needs careful evaluation to exclude EP.

IUDs can be inserted any time in a woman's menstrual cycle as long as she and her clinician are reasonably certain she is not pregnant, and in only few circumstances should this require the performance of a pregnancy test. Guidance for this comes from the US SPR in the form of the Table 2, based on and validated by evidence from family planning programs worldwide.

Table 2 How to be reasonably certain that a woman is not pregnant

A health-care provider can be reasonably certain that a woman is not pregnant if she has no symptoms or signs of pregnancy and meets any one of the following criteria:
Is ≤7 days after the start of normal menses
Has not had sexual intercourse since the start of last normal menses
Has been correctly and consistently using a reliable method of contraception
Is ≤7 days after spontaneous or induced abortion
Is within 4 weeks postpartum
Is fully or nearly fully breastfeeding (exclusively breastfeeding or the vast majority [≥85 %] of feeds are breastfeeds), amenorrheic, and <6 months postpartum

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Increased menstrual flow has long been a known feature of copper IUDs; rarely, however is it of such magnitude to cause clinically apparent blood loss anemia. Use of both the Mirena® and Skyla® is associated with substantially decreased menstrual blood loss and has been utilized as a treatment of menorrhagia, a positive benefit of the LNG. Liberalizing insertion protocols by removing provider barriers to IUD use has the potential to expand the population of IUD users dramatically and reduce the unintended pregnancy rate in the USA.

Subdermal Contraceptive Implants

Subdermal contraceptive implants have been available to women in the USA since 1990 when the FDA approved a 6-rod LNG (216 mg LNG) system for 5 years duration after an extensive track record of safety and efficacy in Europe and Southeast Asia. Despite this, widespread litigation regarding complicated and painful removals prompted the manufacturer to withdraw US distribution in 2002 even though none of the claims were proven and US courts disallowed all class action suits. A single-rod subdermal system, Implanon® developed in Holland by Organon, was introduced into the US market in 2006. This system utilized etonogestrel (3-ketodesogestrel, ENG), the biologically active metabolite of desogestrel, a gonane progestin. The implant is a 4 cm long, 2 mm diameter rod made of ethyl vinyl acetate, and impregnated with 68 mg of ENG such that ENG is released in a controlled fashion over 3 years of use. Implanon® was reformulated by the manufacturer to include 15 mg of barium sulfate such that the implant is now detectable by X-ray and CT scan; it is supplied in a preloaded applicator for single use.

The mechanism of action of ENG as a contraceptive is virtually identical to other progestins by inhibiting ovulation through the ovulation suppression at the level of the hypothalamic-pituitary axis (HPA) and the LH surge [22]. ENG also thickens cervical mucus, inhibiting sperm transport to the upper genital tract, providing additional contraceptive activity. The ENG implant is designed for 36 months continuous use, during which ENG serum levels typically range from 196 pg/ml at the end of 1 year and 156 pg/ml after 36 months; both of these values are above the 90 pg/ml thought necessary to inhibit ovulation. Removal of Nexplanon® is associated with prompt decline in ENG to undetectable serum levels within 1 week; this is consistent with a return to ovulation and previous fertility by 6 weeks after removal. Unlike injectable progestins such as medroxyprogesterone acetate (MPA), serum estradiol (E2) levels are essentially within normal levels.

ENG subdermal implants have demonstrated remarkable contraceptive efficacy, with failure rates approaching zero if pregnancies that were not directly related to contraceptive method failure were eliminated from analysis [23]. In a study from Australia of post-marketing surveillance, 218 confirmed cases of unintended pregnancy were identified while using the ENG subdermal implant. However, 21 % of these patients were found to have been pregnant prior to implant insertion, another 39 % were due to "non-insertion" of the implant itself; only 19 % of the pregnancies were tied directly to method failure. Of these, nearly 20 % were secondary to interactions with medications that are known to accelerate the metabolism of progestins such as carbamazepine. As a result, Nexplanon may not be the best contraceptive choice for patients who require the use of hepatic enzyme inducers [24].

The side effect profile of the ENG subdermal implant is similar in many aspects to that of any progestin-only contraceptive method. The most common side effect leading to implant discontinuation is irregular and unpredictable vaginal bleeding patterns (11 % of patients). Although the most frequent change in bleeding pattern is infrequent bleeding and amenorrhea (50 % of patients), nearly 19 % of users experienced frequent or prolonged bleeding. Manipulation of abnormal bleeding patterns with low-dose CHCs, additional estradiol, or doxycycline has met with limited success. This complication emphasizes the importance of careful pre-insertion counseling and patient selection. Though Nexplanon®

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is only FDA approved for the prevention of pregnancy, it appears that dysmenorrhea improves dramatically in users. About 12 % of patients utilizing the ENG subdermal implant can be expected to experience weight gain in the amount of 1–2 kg over the 36 months of use. While women whose weights were >130 %, ideal body weight was excluded from early clinical trials of the ENG implant; a multicenter clinical trial that included women of all weights found no unintended pregnancies in patients that were overweight or obese [25]. Indeed, the CDC-MEC places the ENG implant into category 1 for patients whose BMI is ≥ 30 kg/m^2, meaning there is no restriction on its use for these women.

Injectable Contraceptives

The injectable contraceptive agent, medroxyprogesterone acetate (DMPA) or Depo-Provera®, has a typical failure rate of 1 per 100 woman-years. One of the reasons for the high efficacy is that each 150 mg injection provides 3 months of protection followed by a 4–6-week grace period before the next injection. Depo-Provera may cause excessive uterine bleeding but amenorrhea is more common. Amenorrhea, secondary to endometrial atrophy, occurs in over 90 % of women who use DMPA for more than 2 years [26]. Use of DMPA does not result in irreversible suppression of ovulation but patients need to clearly understand that there may be a delay in return to fertility. The inhibitory effect of DMPA on the HPA may persist for an extended time after DMPA is stopped resulting in the delayed fertility.

DMPA can be safely initiated immediately postpartum with the first injection given within 5 days of delivery. Other acceptable candidates for DMPA include smokers over age 35 and adolescents. It appears to have little effect on blood pressure or thrombosis.

Use of DMPA in adolescents is not associated with a higher risk of incident sexually transmitted infections. Additionally, women who choose DMPA report an improved quality of life, with secondary amenorrhea contributing to this perception. Adolescents using DMPA have lower incidence of repeat pregnancy at 12 months postpartum compared to those choosing CHCs [27]. The lower pregnancy rates with DMPA may be the result of a higher continuation rate compared to CHCs, although it is not as high as that seen with IUDs.

Side effects including weight gain, nausea, and irregular menstrual cycles are commonly reported. There is a reported association between long-term use of DMPA and depressive symptoms that subsides upon discontinuation [28]. There is no evidence, however, that DMPA use increases risk for postpartum depression. DMPA use results in a decrease in ovarian function and a consequent reduction in estrogen secretion which has been linked to a measurable decrease in bone mineral density (BMD). However, there is no evidence that this BMD decrease confers increased fracture risk for long-term users of DMPA. Consequently, the American College of Obstetricians and Gynecologists (ACOG) recommends that concerns over decreased BMD and potential future risk should not prevent its use beyond 2 years given its demonstrated contraceptive benefits [29].

Emergency Contraception (EC)

When primary contraceptive methods fail, unintended pregnancy may be prevented by the use of either hormone(s), selective progesterone receptor modulators (SPRMs), or IUDs. Postcoital contraceptive methods have been available for many decades now, beginning with the high-dose estrogen regimen (diethylstilbestrol, DES) that was widely used in the 1960s. Described in the 1970s, the Yuzpe regimen employed doses of estrogen and progestin available in standard combination oral contraceptives (COCs) taken by the patient within 72 h of unprotected intercourse [30]. Both of these regimens were fraught with

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significant side effects for patients, not the least of which was extreme nausea and vomiting as a result of the high dose of estrogen. In an effort to avoid these adverse effects, LNG was employed alone in a study from the WHO, showing it to be more effective overall [31]. The second generation SPRM ulipristal acetate (UPA) has been found to have higher efficacy than LNG, even when utilized 5 days after unprotected intercourse [32]. Of all methods of EC, the copper IUD (Cu-IUD) has the highest efficacy when employed for EC, with reported rates of unintended pregnancy <1 % [33].

It is likely that EC interferes with the process of ovulation, modifying tubal transport of ovum and/or sperm to interfere with sperm capacitation, and producing luteolysis. EC is only effective during a limited portion during a woman's menstrual cycle. Spermatozoa have a limited life span (120 h) within the female reproductive tract, and the human oocyte survives a mere 12–24 h postovulation. This results in a fertile window extending from 5 days prior to ovulation to 1 day after, the highest rates of conception occurring within 2 days prior to ovulation. Copper ions are released rapidly into the female genital tract shortly after insertion of an IUD such that their concentration reaches levels that are directly toxic to spermatozoa and hence results in decreased mobility, viability, and sperm capacitation and penetration. It is not known whether the Cu-IUD interferes with human blastocyst implantation as there are no in vivo human studies for ethical reasons. Both UPA and LNG negatively affect follicular development and ovulation. LNG can inhibit the LH surge, especially when given 2 or 3 days prior to ovulation. UPA has been shown to inhibit 100 % of follicular ruptures if given prior to the LH surge. The effect of LNG on the LH surge is limited by a narrow time window; if taken prior to the selection of the dominant ovarian follicle, LNG can prevent follicular rupture and ovulation. Taken after LH begins to rise, it cannot prevent ovulation and is ineffective in preventing pregnancy. UPA, however, has a direct inhibitory effect on follicular rupture, accounting for its effectiveness when LH has already begun its rise.

EC efficacy may be compromised in women with higher body mass index (BMI). Though the study was not intended to examine the effect of BMI on EC efficacy, a meta-analysis of two studies comparing the efficacy of LNG and UPA for EC demonstrated markedly decreased efficacy with higher BMI for both. Patients with BMI >26 kg/m^2 who used LNG for EC had the same expected pregnancy rate as if they had not used anything. UPA use in patients with BMI > 35 kg/m^2 was associated with a similar failure rate [34]. There has been considerable debate over the meaning of these findings but there are no published studies to date that refute the BMI effect. Expert opinion appears to favor either the insertion of a Cu-IUD or administration of UPA in obese patients.

The timing of EC is critical for successful avoidance of unintended pregnancy; all oral ECs should be administered and taken as soon as possible after intercourse that is either unprotected or compromised by contraceptive method failure (condom rupture, etc.). The LNG regimen, which consists either of a single 1.5 mg pill (Plan B One-Step®) or 2 0.75 mg pills (generic, Take Action®, and others) taken together, can be effective up to 5 days after unprotected intercourse. UPA is available as a single 30 mg tablet, currently marketed as Ella®. However, effectiveness appears to decline over time from intercourse. (1) Recent data suggests that insertion of a Cu-IUD for EC may be effective at any time during the menstrual cycle.

The only known contraindications to EC are pregnancy and allergy to any of the components in them. It is unknown whether efficacy is compromised in the presence of other medications that induce hepatic enzyme systems responsible for metabolism of steroid hormones. EC with LNG or UPA may shorten cycle length by 1 and 2 days, respectively. Menstrual bleeding may increase following the insertion of a Cu-IUD as might be expected; however, counseling can help patients anticipate and accommodate such changes. Whereas nausea and vomiting were hallmarks of the high-dose estrogen and Yuzpe regimens, few patients utilizing LNG or UPA experience significant nausea.

LNG EC is now available in the USA without prescriptive or age restrictions to women and men, which has the potential to dramatically expand its use; it is relatively inexpensive. UPA is only available in the USA by prescription, a substantial barrier to its use. Even though the Cu-IUD carries the highest EC

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efficacy, getting one inserted in a timely fashion can be problematic; patients must navigate multiple logistic issues, none the least of which is provider ignorance of its use for EC.

Combined Hormonal Contraceptives (CHCs)

This category includes combined oral contraceptives (COCs), transdermal patch, and vaginal ring. All three forms work by suppressing ovulation and follicle maturation and as spermicides by thickening cervical mucus. All three forms are considered to be moderately effective contraception: with typical use, the failure rate is 6–12 pregnancies per 100 woman-years [35].

All CHCs contain an estrogen and a progestin in varying doses and schedules. The estrogen is most commonly ethinyl estradiol and can range from 20 to 50 micrograms (mcg). The progestin is classified by steroid structure, potency, and when the form became available, i.e., first generation, second generation, etc. Given the multitude of choices that have arisen with varying levels of estrogen and progestin, it is helpful to use an aide when discussing CHCs with patients such as Table 3. A pill can be selected that minimizes undesired side effects while maximizing non-contraceptive benefits.

Initiating the CHC the day the prescription is received is preferable to waiting; women are more likely to continue onto the second pack of pills, and they are less likely to become pregnant in the first 6 months of use [36]. All COCs must be taken daily and require a prescription.

Common side effects include dizziness, nausea, breast tenderness, change in menstruation, and change in mood. More serious side effects include elevation of blood pressure, venous thromboembolic disease (VTE), and stroke. While CHCs do increase the risk of VTE from 4–5 per 10,000 women-years to 9–10 per 10,000 women-years, the absolute risk is still small compared to the VTE risk associated with pregnancy and the postpartum period, 29 and 300–400 per 10,000 women-years, respectively. The evidence for increased risk of VTE based on progestin has been conflicting and is most likely not clinically significant.

The contraindications to the use of CHCs include women with active breast cancer, decompensated cirrhosis, acute VTE, history of nontraumatic VTE, prolonged immobilization, diabetes with micro- or macrovascular complications, migraine with aura, any migraine in women over 35 years old, vascular disease or uncontrolled hypertension, ischemic heart disease, malignant liver tumors or hepatocellular adenoma, decreased cardiac function including mild dysfunction if less than 6 months postpartum, less than 21 days postpartum, women over 35 years old who smoke more than 15 cigarettes per day, complicated organ transplant, stroke, systemic lupus erythematosus with positive antiphospholipid antibodies, hypercoagulable disorders, complicated valvular heart disease, and acute viral hepatitis.

There are many non-contraceptive health benefits associated with COCs (and by inference the transdermal patch and vaginal ring). The following benefits have Level A evidence: reduction in risk of endometrial and ovarian cancer [37], reduced blood loss in women with normal menses or menorrhagia, treatment of dysmenorrhea, acne, treatment of premenstrual dysphoric disorders, and for continuous long-term suppression of menstruation [38]. Women who take COCs reduce their risk of endometrial cancer by 50–80 % with longer duration of use resulting in greater risk reduction. Similarly, the greater the duration of COC use, the greater the decrease in ovarian cancer risk. This decrease in risk corresponds to a 20 % reduction for each 5 years of use. COCs can reduce blood loss by 40–50 % and dysmenorrhea in 70–80 % of users.

COCs can be used for extended cycles instead of monthly cycles. Currently Seasonale®, Seasonique®, and Lybrel® are the only FDA approved COCs for this use. However, any COC can be utilized for extended cycle use. Typically, 3 packs of pills are dispensed and taken consecutively followed by a 7 day placebo period. The efficacy is the same as for monthly cycling but there is an increased risk for

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Table 3 Combined oral contraceptives: Side effects, benefits, and special considerations

Clinical situation	Explanation	Contraceptive option
Nausea, breast tenderness, bloating, headache, melisma, or increased blood pressure while on COC	Too much estrogen	EE 30 mcg – norethindrone acetate 1.5 mg (Junel, Loestrin, Microgestin) or
		norethindrone 0.35 mg (Camila, Errin, Jolivette, Micronor, Nor-QD, Nora-BE)
Spotting/bleeding, especially early or midcycle, hypomenorrhea	Not enough estrogen	EE 35 mcg – norgestimate 0.25 mg (Ortho-Cyclen, Mononessa, Previfem, Sprintec)
Mood changes, fatigue, as well as breast tenderness and headache	Too much progestin	EE 20 mcg – levonorgestrel 0.1 mg (Alesse, Aviane, Lessina, Levlite, Lutera) or
		EE 35 mcg – norethindrone 0.4 mg (Ovcon-35, Ovcon-35 chewable)
Breakthrough spotting or bleeding late in cycle	Not enough progestin	EE 20, 30, 35 mcg – norethindrone 1 mg (Estrostep Fe, Tri-Legest Fe) or
		EE 25 mcg – norgestimate 0.18, 0.215, 0.25 mg (Ortho Tri-Cyclen Lo, Tri-Lo-Sprintec, Trinessa)
Weight gain, polyphagia, acne, hirsutism, decreased libido, breast growth and tenderness	Too much androgen	EE 30 mcg – drospirenone 3 mg Yasmin, Ocella, Zarah) or
		EE 35 mcg – ethynodiol diacetate 1 mg (Demulen 1/35, Kelnor 1/35, Zovia 1/35)
Breastfeeding and/or <1 month postpartum	Increased risk of VTE from estrogen. Theoretical effect on breast milk supply	norethindrone 0.35 mg (Camila, Errin, Jolivette, Micronor, Nor-QD, Nora-BE)
Need to minimize effect on cholesterol (hyperlipidemia, hypertension, diabetes)	All have favorable lipid profiles	EE 30 mcg – desogestrel 0.15 mg (Ortho-Cept, Desogen, Reclipsen) or
		EE 35 mcg – norgestimate 0.25 mg (Ortho-Cyclen, Mononessa, Previfem, Sprintec) or
		EE 35 mcg – norethindrone 0.4 mg (Ovcon-35, Ovcon-35 chewable)
		EE 35 mcg – norethindrone 0.5 mg (Brevicon, Modicon, Necon, Nortrel)
Patient taking medications that interact with hepatic enzyme metabolism:	Medication interactions	Preferred reversible method is IUD or standard dose (> = EE 30 mcg) COC
Antiretroviral therapy		
Ritonavir-boosted protease inhibitors		
Anticonvulsant therapy		
Phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine		
Lamotrigine		
Antimicrobial therapy		
Rifampicin or rifabutin therapy		

See Refs. [4, 7, 9, 13, 14, 38]

breakthrough bleeding especially during the first 3 month cycle. The benefits include decreased pelvic pain, blood loss, and headaches with improvement in mood. This is also true for extended use of the transdermal patch and vaginal ring.

The transdermal hormonal patch contains norelgestromin and ethinyl estradiol (Ortho Evra®). A patch containing 6.00 mg norelgestromin and 0.75 mg ethinyl estradiol is placed on the skin of the buttocks,

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abdomen, upper torso, or upper outer arms weekly for 3 weeks followed by a patch-free week which produces a withdrawal bleed. Each patch releases 150 μg of norelgestromin and 20 μg of ethinyl estradiol daily. It leads to higher plasma levels of hormones than typical COCs but does not have the peaks and troughs associated with COC use. It functions in the same manner as combination oral contraceptives but is more convenient in a transdermal route for some women lasting for 7 days. It can be started on days 1–5 of the menstrual cycle. If started after day 5, backup contraception should be used for 7 days.

Common side effects are local skin irritation, breast tenderness, breakthrough bleeding, headache, and nausea. These typically resolve after 1–3 cycles much like the side effects of COCs. The risks, contraindications, and benefits for the transdermal patch are the same as for COCs. VTE risk is similar to that of COCs. It is unclear whether the increased serum concentration of estrogen that occurs with the patch compared to COCs increases the overall VTE risk.

The final option for combined hormonal contraception is a flexible vaginal ring comprised of ethinyl estradiol and etonogestrel (NuvaRing®). It delivers 0.015 mg ethinyl estradiol and 0.120 mg of etonogestrel daily. The ring is placed circumferentially around the uterine cervix for 3 weeks and then removed for 1 week during which a withdrawal bleed occurs. Because hormones are delivered in close proximity to the uterus and ovaries, a lower dose can be used. The vaginal ring offers the lowest dose of hormones of any CHC and avoids first-pass hepatic metabolism. As with COCs, it may be used for extended or continuous cycling with placement of a new ring after week three, but this method is not FDA approved. If removed for more than three hours during weeks 1–2, backup contraception is required. It may be started on days 1–5; however, backup contraception is required for 7 days if started on days 2–5 or if initiated asynchronous to the end of the menstrual cycle.

Common side effects are similar to COCs but also include increased vaginal discharge and irritation. Risks, contraindications, and benefits are equivalent to those of COCs. While the ring results in the lower serum concentration of hormones compared to COCs or the transdermal patch, it is unclear whether this effect is clinically significant. Of note, in clinical trials, women who weighed more than 90 kg had a significantly higher failure rate than lower-weight women. This rate is similar to the failure rate for COCs in women over 90 kg and should not preclude use of either method but appropriate risk counseling should be given.

Barrier Methods

The condom is the oldest form of barrier contraception and has benefits due to its inherent safety as well as potential protection from STIs. The ability of the condom wall to maintain its integrity throughout intercourse is critical to its effectiveness. It has been demonstrated that condom breakage occurs in approximately 1 of 100 acts of intercourse. Factors associated with breakage included vaginal intercourse and minimal foreplay. Data has shown that consistent use of condoms can reduce HIV transmission by up 80 % and non-viral STIs by 59 % [39].

The contraceptive diaphragm is a dome-shaped rubber cup attached to a flexible rim. The rim enables the dome to make a tight seal with the vaginal wall to provide a barrier to sperm and infectious agents. The diaphragm also prevents cervical mucus from neutralizing vaginal acidity, so the vaginal environment remains hostile to the sperm. The diaphragm is inserted by the woman herself vaginally before intercourse so the posterior rim rests behind the cervix in the posterior fornix and the anterior rim fits snugly behind the symphysis pubis. Spermicidal jelly, placed into the dome and around the rim before insertion, helps create a seal between the diaphragm rim and the vaginal wall and adds to its contraceptive efficacy.

Diaphragms are manufactured in various shapes to accommodate the anatomic variance of the female pelvis. They must be properly fitted to be effective, as diaphragms that are too big or too small are not

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effective in preventing pregnancy. Failure rates have been reported between 1 and 19.4 per 100 women-years. Given the challenges in assessing proper fit, education on use, and the development of more convenient, higher efficacious options for women, diaphragms represent at best fair contraceptive effectiveness and use rates have declined.

Spermicides

Spermicides are most often used in conjunction with other forms of contraception, namely, the condom and diaphragm. Spermicides are rarely used as a single contraceptive agent despite that they are simple to use and readily available. Spermicidal agents consist of two components: (1) an inert base (foam, cream, jelly, film, suppository, tablet) that ensures dispersion and holds the spermicidal agent in the vagina and (2) the spermicidal agent, usually nonoxynol-9. Failure rate among typical uses is high, 28 per 100 women per year.

Permanent Contraceptive Methods

Vasectomy

Vasectomy is a safe and effective form of contraception. Performed as an outpatient procedure, it has a very low complication rate. Concerns about association with prostate and testicular cancer in vasectomized men are unfounded. Most men achieve azoospermia within 4 months of the procedure, with long-term sterility greater than 99 %.

Tubal Sterilization

Tubal ligation remains a common method of family planning in the USA. Almost 50 % of female permanent contraceptive procedures occur while women are hospitalized for another surgery or childbirth. The gold standard of female permanent contraception remains either tubal ligation at the time of Cesarean section or interval via laparoscopy or minilaparotomy. A number of tubal occlusive techniques are available for tubal interruption, but bipolar cautery remains the mainstay. Hysteroscopic transcervical tubal sterilization has recently gained popularity, though long-term studies are not yet available that show comparable efficacy with laparoscopic techniques. Because of the permanence of these methods, it is important for patients to think carefully about whether any change such as death or separation from a partner or from a child would make them regret the choice.

Natural Family Planning

Natural family planning (NFP) methods may be useful for those who wish to avoid hormonal, barrier, and surgical methods of contraception. The basis for these methods involves abstinence from intercourse during periods of fertility and requires either recognition or detection of ovulation and the assumption that ovulation occurs only once during the same menstrual cycle. Methods of ovulation detection may incorporate charting cervical mucus changes (the ovulation or Billings method), a combination of mucus charting, symptom identification, and confirmation of a rise in basal body temperature to confirm postovulatory infertility (the symptothermal method) and urinary testing for luteinizing hormone levels.

The Creighton Model Natural Family Planning System is a standardized system of teaching couples how to perform the method accurately. Proponents of NFP cite the absence of side effects of artificial

methods of contraception, the benefits of increased communication between partners, and the opportunity to explore aspects of the sexual relationship other than intercourse. This method is not opposed by any religious organization but does require motivated couples, careful education, and close follow-up to optimize efficacy. Of the NFP methods, only the lactation amenorrhea method (LAM) has been acknowledged as highly effective, but use is limited to very specific and temporary criteria: exclusive breastfeeding, postpartum <6 months, with amenorrhea [40]. Reported pregnancy rates for a typical user of NFP are 24–30 %. Given the presence of many other methods with greater efficacy, NFP should not be recommended unless no other contraceptive method is acceptable to the patient.

Community Issues

Barriers to contraceptive access remain including maintaining insurance coverage, understanding benefits, securing an appointment with a provider, and obtaining prescriptions (1). There is evidence that Title X funding improves access to contraceptive services especially for forms that require advanced training and skill such as LARCs and vasectomy (2). For women with insurance coverage, access to low-cost or free contraceptives has improved with the passage of the Patient Protection and Affordable Care Act which requires this coverage. For women without insurance coverage, many large retail pharmacies offer COCs or POPs at low cost, particularly when a 90-day supply is prescribed. Emergency contraceptives have also become more readily available after a 2013 decision by the US Food and Drug Administration that made Plan B One-Step® available over the counter without a prescription to anyone of childbearing potential. A generic version is approved for ages 17 and older, but proof of age is not required.

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Vulvovaginitis and Cervicitis

Jennifer Bain

Contents

Vulvovaginitis and cervicitis refer to inflammatory and/or infectious disease processes of the female genital tract: vulva, vagina, and cervix. Symptoms can include genital itching, pain or discomfort, edema, dysuria, vaginal discharge, odor, and in more severe cases pelvic pain. Female genital complaints are quite common in a family medicine practice so familiarity with the workup and treatment is important. The symptoms can be nonspecific, and there is considerable overlap of presenting features regardless of the etiology of the process. In many cases the patients have already attempted self-diagnosis and even treatment with home remedies or over-the-counter products and medications. Given the nonspecific nature of the symptoms, those self-diagnoses can often times be incorrect, and the products or measures the patient has employed in their attempt to treat those symptoms can lead to more inflammation and exacerbate the condition. It is imperative, therefore, to take a detailed history, perform a focused but complete physical exam, and utilize laboratory measures, including microscopy, in order to arrive at the correct diagnosis.

The most common etiologies for vulvovaginitis and cervicitis include both sexually and nonsexually transmitted diseases, and coinfections are not uncommon. Depending on the disease process involved, the symptoms may be restricted to just one of the areas of the genitals (e.g., the vulva) but often can include more than one or all and be difficult for the patient to determine exactly. The most common causes of vaginal

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complaints, particularly in reproductive aged women, include bacterial vaginosis, candidal vaginitis, and trichomoniasis. Cervicitis is often one of the sexually transmitted diseases (STDs), such as gonorrhea or chlamydia. The keratinized epithelium of the vulva can be affected by other generalized skin disorders (such as atopic dermatitis or psoriasis) and mycotic infection as well as masses. However, there is considerable overlap and any one of these processes can causes symptoms in any or all of the particular areas of the female genitals. In general, testing for STDs (in particular gonorrhea and chlamydia) should be obtained during the evaluation given considerable overlap in the clinical presentations and the prevalence of coinfections.

The vulva is composed of keratinized stratified squamous epithelium, whereas the vaginal and the ectocervix mucous membrane is nonkeratinized squamous epithelium. There is a transition in the epithelium from the labia to the vestibule. The normal vaginal environment contains lactobacilli that convert the glycogen from these cells into lactic acid and hydrogen peroxide, maintaining the acidic pH (around 4.0) characteristic of the healthy premenopausal woman's vagina. This acidic environment helps to prevent the overgrowth or invasion of pathogenic organisms. Disruption of this normal balance of chemical and biological elements can then lead to infection or inflammation causing vulvovaginitis or cervicitis.

Office Evaluation

Obtaining a good history can be complicated by some patient's reluctance to discuss these issues; often the patients are embarrassed or simply uncomfortable discussing symptoms in the genital area and may not know how to describe their symptoms well. In addition to the usual characteristics of the complaint (their best description of symptoms and their and duration), exacerbating and alleviating factors and any associated symptoms (dysuria, dyspareunia, pelvic pain, fever), it is important to inquire about any previous episodes (and treatments), involvement of any other areas of the body, treatments attempted at home (their success or lack thereof), sexual behaviors (number and gender of partners, as well as if anal, oral, or vaginal penetration is involved), and partner symptoms. Comorbidities can be a complicating factor, as well (diabetes mellitus (DM), human immunodeficiency virus (HIV)).

A complete physical exam should be performed, including a thorough pelvic exam, abdominal or costovertebral tenderness on palpation; close inspection of the skin of the entire area including separation of the labia, noting any atypical findings of the skin or genitals or surrounding structures; and a vaginal speculum examination, noting the presence of any odor, lesions, discharge, or other findings of the vagina and cervix. Document the presence or absence of any discharge and its characteristics, such as color, consistency (thin, thick, frothy, clumpy), origin (if from the cervical os, adherent to the vaginal walls, etc.), or odor; friability or bleeding from the cervix; and any tenderness or masses on the bimanual exam (cervical motion tenderness; tubal, ovarian, uterine, or adnexal tenderness).

Vaginitis

The diagnosis may be narrowed after a thorough history and physical exam described above; however, the identification of the true cause of the patient's symptoms is not possible without performing a simple laboratory evaluation due to the similarities in signs and symptoms. Vaginal specimens can be collected during the speculum exam noted above, including testing for sexually transmitted diseases (STDs) and swabs for preparing a wet mount and KOH specimen. Depending on the method used for the specimen identification (nucleic acid amplification, culture, PCR, etc.), the samples may be taken from the cervical os or the vaginal side walls. There is typically pooling of fluids (mucous and semen) in the posterior fornix, so the best sample is not obtained from this site. The wet mount is prepared using a cotton-tipped swab to collect a specimen from the vaginal side wall. The swab can then be touched directly onto pH paper to determine the pH of the vaginal fluid, then either placed in a test

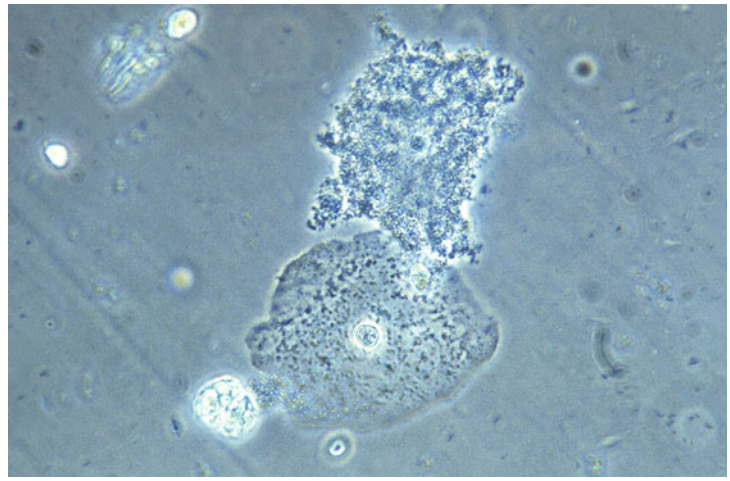

Fig. 1 Two epithelial cells on vaginal wet mount preparation: one normal and the other with the surface studded with coccobacilli, termed clue cell, as seen in bacterial vaginosis (Public Health Image Library from the CDC)

tube with about three drops of saline and a drop is placed on two slides or the swab can directly place the drop of the vaginal specimen on the slides with a drop of saline on one; on the other of these slides a drop of 10 % KOH is placed and then a cover slip is placed over each to examine under the microscope. Before covering the KOH specimen, wafting the aroma from the slide to the nose of the examiner is termed the whiff test and can identify identifying scents associated with certain infections. The best visualization of the elements under investigation would be with the use of the low power (10x) first and then high power (40x) to allow viewing of the smaller elements.

In the case of a healthy vaginal environment, the vaginal discharge is white or transparent, thick, or thin and mostly odorless, and the vaginal pH will be in the normal range (4.0–4.5). Microscopy will show epithelial cells (large, round to somewhat oval cells, sometimes folded, with a relatively small nucleus and clear to somewhat granular cytoplasm) with occasional polymorphonuclear (PMN) cells (or leukocytes; smaller, rounded to oval cells with segmented, larger nuclei), occasional erythrocytes (RBCs: small round cells with no nuclei), and lactobacilli (small rod-shaped bacteria) and even sperm can be seen at times (very small motile organisms with the characteristic tail). When there is an alteration in the healthy vaginal chemical or biological environment, there may be other findings on microscopy: clue cells (epithelial cells that are covered in small, round bacteria, particularly prominent at the edges of the cells) (Fig. 1), fungal elements (buds, hyphae, and pseudohyphae; Fig. 2), a large proportion of PMNs, flagellated trichomonads (Fig. 3), a lack of lactobacilli or PMNs; and higher numbers of basal cells (smaller epithelial cells with a higher nucleus-to-cytoplasm ratio). Identifying these elements on the laboratory evaluation will assist greatly in the accurate diagnosis of the etiology of the patient's complaints.

Bacterial Vaginosis

Bacterial vaginosis (BV) is the most common cause of vaginal complaints in women [1], though many women can be asymptomatic. There is no true inflammation, hence the term vaginosis, rather than vaginitis, and typically there is no vulvar involvement. BV involves a shift in the normal vaginal flora with a lack of lactobacilli and with an overgrowth of anaerobic organisms such as *Gardnerella vaginalis*, *Haemophilus* species, *Bacteroides*, *Mycoplasma hominis*, *Ureaplasma urealyticum*, *Mobiluncus*, and others. The exact mechanism of the alteration in the flora is unclear, but the lack of the lactobacilli raises the pH, no longer prohibiting the growth of the offending anaerobic bacteria, and a massive overgrowth occurs. It appears there is a biofilm [2] produced by the *Gardnerella* on the vaginal side walls that other bacteria then adhere. These

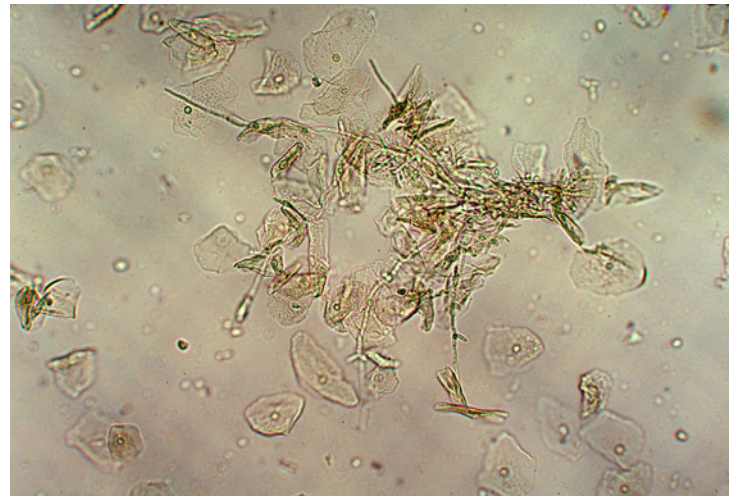

Fig. 2 Vaginal wet mount preparation showing epithelial cells and pseudohyphae of *Candida albicans* (Public Health Image Library of the CDC)

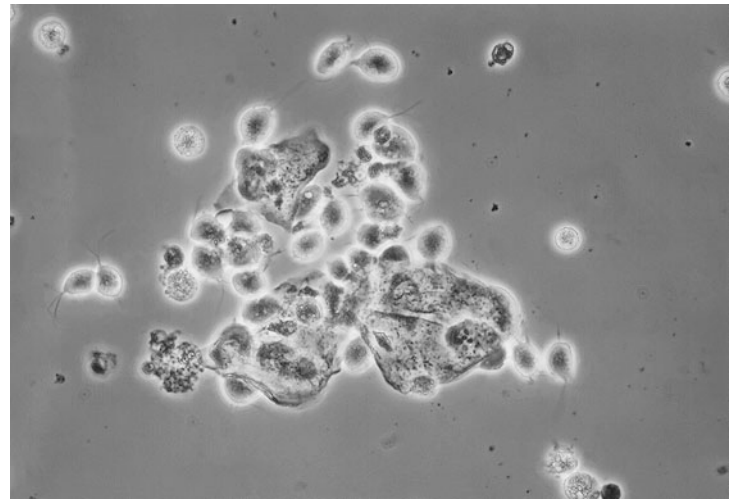

Fig. 3 Vaginal wet mount preparation showing the flagellated trichomonads (Public Health Image Library of the CDC)

organisms produce proteolytic carboxylase enzymes that break down the vaginal peptides and produce amines that give the characteristic "fishy" odor noted during the whiff test. There is desquamation of these cells to produce the classic clue cells (Fig. 1) seen on the wet mount.

BV is not considered a sexually transmitted infection, but sexual activity does seem to be a factor: women with new or multiple sexual partners are at a higher risk, and there is a decrease in risk with the use of condoms and having monogamous sexually active long-term relationships. There is a high prevalence in women who have sex with other women, particularly with new or multiple partners. Other risk factors include douching (which can eliminate the lactobacilli that help to maintain the healthy acidic vaginal environment), smoking, and possibly a genetic component to susceptibility.

The prevalence is hard to determine, as this is not a reportable disease, and can vary considerably based on the population studied [3]. It is commonly found in women of reproductive age, rarely in postmenopause and not in children. There may be no symptoms or just the complaint of an unpleasant odor, worse after intercourse or during menses. A vaginal discharge may be present that is typically thin and off-white (gray or

yellow). Dysuria, dyspareunia, and pelvic pain are not usual complaints and, if present, may be a sign of mixed vaginitis or coinfection. On physical exam a homogenous, thin, sometimes malodorous vaginal discharge may be seen, typically adherent to and smoothly coating the vaginal walls. Acute cervicitis, with a mucopurulent discharge from the cervical os, and even cervical motion tenderness can be seen if there has been assent of the infection into the cervical canal and even to the upper portions of the genital tract, though it is more likely a sign of coinfection.

Diagnosis of BV is made primarily by characteristic laboratory findings, elevated pH, and the characteristic findings seen on microscopy: clue cells with a lack of lactobacilli and PMNs. Amsel's criteria is used when microscopy is available and is considered diagnostic of BV if any three of the following are present: characteristic vaginal discharge (thin, off-white, homogenous, smoothly coating the vaginal walls), elevated pH (>4.5), predominance of the epithelial cells (>20 %) that are clue cells on saline wet mount, and positive whiff test (fishy odor with the addition of 10 % KOH to the vaginal sample). Gram stain is considered the gold standard of diagnosis; however, this requires more time, resources, and expertise. Utilizing Gram stain as the gold standard, Amsel's criteria is >90 % sensitive and 77 % specific [4]. A shift in vaginal flora can be seen on a pap smear specimen; however, the sensitivity is low and should not be relied upon for diagnosis. There is no indication to treat asymptomatic patients with this finding on the pathology report.

There are some serious health consequences as a result of BV: increased risk of preterm delivery in pregnancy, endometrial bacterial colonization and endometritis, pelvic inflammatory disease (PID), postpartum fever, post-hysterectomy vaginal cuff cellulitis, postsurgical abortion infection, and increased risk for acquisition of other STDs (HIV, HSV 2, gonorrhea, chlamydia, and trichomonads). The Centers for Disease Control and Prevention (CDC) does not currently recommend treatment of asymptomatic women, only those with the symptoms and diagnostic criteria above, as there is insufficient evidence of the benefit of treating asymptomatic women at this time [5]. Though this is not considered a sexually transmitted infection, it is a common finding for those women presenting in such a scenario; and the treatment guidelines here are consistent with those of the CDC, in their Treatment Guidelines for Sexually Transmitted Diseases [5].

Treatment of BV is recommended in symptomatic women for relief of symptoms and in presurgical patients undergoing gynecologic procedures (hysterectomy and surgical abortion); partner treatment is not recommended. Several oral and topical regimens are acceptable and effective: metronidazole (Flagyl) 500 mg orally twice daily for 7 days; metronidazole gel 0.75 %, one full applicator (5 g) intravaginally once a day for 5 days; or clindamycin cream 2 %, one full applicator (5 g), intravaginally at bedtime for 7 days. Alternative regimens include tinidazole (Tindamax) 2 g orally once daily for 2 days, tinidazole 1 g orally once daily for 5 days, clindamycin (Cleocin) 300 mg orally twice daily for 7 days, or clindamycin ovules 100 mg intravaginally once at bedtime for 3 days. Oral treatment is as effective as topical, but associated with more side effects, such as metallic taste, nausea, neutropenia, peripheral neuropathy, some drug reactions, and a disulfiram-like effect (nausea/vomiting/diarrhea) with concurrent consumption of alcohol. Clindamycin cream can weaken condoms and either route can be associated with the development of pseudomembranous colitis.

Treatment recommendations for women with bacterial vaginosis in pregnancy include oral medications for those who are symptomatic: metronidazole, either 500 mg twice daily or 250 mg three times daily, or clindamycin 300 mg twice daily, all for 7 days. Despite metronidazole crossing the placenta, there has been no good evidence of teratogenic effects in pregnancy. Though pregnant patients with bacterial vaginosis have an increased risk of complications including premature rupture of membranes and preterm delivery, postpartum endometritis, and post-cesarean wound infection, a routine screening and treatment regimen has not been found to effectively decrease these rates. Topical treatments are

preferred in breast-feeding women, to decrease concentrations of drugs in breast milk and thus infant exposure and complications such as diarrhea and candidal infections due to alteration of gut flora or other toxicities.

Follow-up after treatment is unnecessary if symptoms resolve, though recurrence of BV is very common: usually within the first year after treatment and often associated with a new sexual partner. This could be the result of reinfection or persistence of BV-associated organisms or a failure to restore the normal vaginal flora (in particular a lack of lactobacilli recolonization of the vagina). Simply retreating can be sufficient, particularly if compliance with the initial regimen may have been an issue. If the patient has continued recurrences (>3 in 12 months), suppressive therapy may be indicated: twice weekly metronidazole gel for 4–6 months or oral nitroimidazole followed by intravaginal boric acid (600 mg nightly) and suppressive metronidazole gel. Caution: boric acid can cause death if taken orally. Prevention measures include patient education regarding identifying the presence of the infection (recognizing the odor and/or discharge), risk reduction with consistent use of condoms, limiting the number of sexual partners, and avoiding douching. The use of probiotics (supplemental lactobacillus in various forms) has not been shown to be beneficial.

Candidiasis

The second most common cause of vaginal infection is due to candidiasis [6] (commonly called a "yeast infection") or vulvovaginal inflammation in the presence of candidal species. The presence of candidal species is not considered abnormal as they are typically found in the normal flora of the vagina and skin of healthy women. It is thought there is some disruption to this normal environment that allows the organism to overgrow and cause infection. The diagnosis requires the presence of vulvovaginal inflammation with pruritus of the vulva and vagina, a common complaint. The symptoms are the result of overgrowth of *Candida* and penetration of the superficial epithelial cells. *Candida albicans* is responsible for the great majority of these infections, less commonly with other species such as *C. glabrata* and *C. parapsilosis* [6]. All species produce similar vulvovaginal symptoms, though usually less severe with *C. glabrata*.

Sexual activity is not believed to play a role in the transmission of vulvovaginal candidiasis (VVC). Though many patients have no identifiable risk factors or precipitating condition, there are risk factors that appear to increase the likelihood or frequency of infections [7]. Antibiotic use causes inhibition of the normal bacterial flora and can allow the growth of fungal organisms leading to symptomatic infection. Immunosuppression as a result of medical conditions (such as poorly controlled diabetes or HIV) or use of medications (glucocorticoids and other immunosuppressive agents) has been linked to the development of this infection. The condition is so common that routine screening for any of these factors is not necessarily indicated, unless there is persistence of infection. Behavioral factors can play a role as well: douching (which can alter the normal biological and chemical vaginal environment), use of tampons or pads, and wearing tight and/or synthetic clothing and use of certain contraceptives (such as the vaginal sponge) all seem to increase the rate of this infection.

The prevalence of VVC is difficult to determine given that it is not a reportable infection, and there are often self-diagnosis and treatment with readily available and highly utilized over-the-counter medications, though it does appear that most women are affected with this infection at least once in their lifetime [5, 8]. When patients do present for medical attention, they are often treated merely based on symptoms without confirmation by microscopy or culture. The clinical presentation is typically that of vulvovaginal pruritus, with accompanying burning, soreness, and irritation. Dysuria (usually externally rather than internally) and dyspareunia can accompany the symptoms. There may or may not be a reported vaginal discharge, but if so it is typically described as white and thick or "clumpy," usually with no abnormal odor.

The characteristic findings on physical exam consist of erythema of the vulva and vaginal mucosa, with possible edema, vulvar excoriations, and even fissures. There may be little or no discharge, and if present it is often thick, white, and curd-like (though other cases, it is thin and watery) with no or minimal odor. The cervix typically does not show involvement other than adherence of any discharge that may be present in the vaginal vault. The clinical presentation however can be quite variable and have considerable overlap with other etiologies of vulvovaginitis.

The diagnosis of VVC is made in women with the characteristic findings of vulvovaginal inflammation and confirmed with the presence of *Candida* on the wet mount. The vaginal pH is usually normal, so if abnormally elevated, coinfection or an alternate etiology should be considered. Microscopic findings on wet mount include the presence of budding yeast (oval cells) and pseudohyphae (chains of cells) (Fig. 2). The addition of 10 % KOH to the vaginal sample, which breaks down the epithelial and other cell walls, can allow better visualization of the fungal elements. During inspection of the wet mount, the presence of clue cells or motile trichomonads should be excluded as a concurrent or alternate infection. Routine culture is not typically helpful as it may merely indicate the presence of colonization of *Candida*, not infection. It is more helpful in the setting of resistant or recurrence of candidal infection. There is no other point of care testing that is available or of proven benefit in diagnosing this condition. Pap smear pathology reports may indicate the presence of candidal species; however, again this may merely indicate the colonization of the vagina with this organism and not the presence of infection. There is no indication to treat asymptomatic women in these cases.

Treatment of VVC is for relief of symptoms and based on the classification: complicated or uncomplicated [5]. Uncomplicated candidiasis episodes are sporadic or infrequent with mild to moderate symptoms in women with a normal immune system that is likely to be due to *C. albicans*. Complicated candidiasis involves severe symptoms and recurrent episodes in immunocompromised women and is more likely to be caused by non-*C. albicans* species. Uncomplicated cases typically respond to all azole therapies (oral or topical) within a few days, whereas complicated cases take longer to respond. In either case, partner treatment is not indicated. Over-the-counter topical intravaginal treatments in uncomplicated cases include butoconazole (Gynazole-1) 2 % cream, 5 g daily for 3 days; clotrimazole (Gyne-Lotrimin) 1 % cream, 5 g for 7–14 days; clotrimazole 2 % cream, 5 g for 3 days; miconazole (Monistat) 2 % cream, 5 g for 7 days; miconazole 4 % cream, 5 g for 3 days; miconazole 100 mg, vaginal suppository daily for 7 days; miconazole 200 mg, vaginal suppository daily for 3 days; miconazole 1,200 mg, vaginal suppository for 1 day; or tioconazole (Monistat 1Day) 6.5 % ointment 5 g for 1 day. Prescription intravaginal agents include butoconazole 2 % cream 5 g for 1 day, nystatin 100,000-U vaginal tablet for 14 days, terconazole (Terazol) 0.4 % cream 5 g for 7 days, terconazole 0.8 % cream 5 g for 3 days, or terconazole 80 mg vaginal suppository for 3 days. The only oral agent is fluconazole (Diflucan) 150 mg tablet in a single dose, which maintains therapeutic concentrations in vaginal secretions for at least 72 h. As all are equally as effective, patient preference is often the deciding factor, with the oral medication associated with more side effects and drug interactions, though in the generic form may be less expensive than the over-the-counter treatments.

Complicated VVC is involved in approximately 10–20 % of cases; and recurrent infection is usually defined as four or more episodes in a year [5]. Treatment requires longer therapy: 7–14 days of topical therapy or 100, 150, or 200 mg oral fluconazole every third day for a total of three doses followed by maintenance therapy with oral fluconazole once weekly for 6 months or topical therapy intermittently for the same time frame. Severe VVC typically does not respond to shorter treatment regimens so recommendations are for 7–14 days of topical therapy or oral fluconazole 150 mg repeated in 72 h. Resistance is unusual, and when suspected culture should be performed and treatment with a non-fluconazole therapy for 7–14 days first-line or 600 mg boric acid

intravaginally daily for 14 days for recurrences. In an immunocompromised host, 7–14 days of topical therapy is recommended.

Candidal vulvovaginitis is not associated with adverse outcomes in pregnancy, so treatment is indicated only for relief of symptoms. Only topical regimens (clotrimazole or miconazole for 7 days) are recommended as there have been case reports of certain birth defects with the use of oral azoles, particularly in the first trimester [9]. In breast-feeding patients, both oral and topical treatments are safe and effective as there appear to be no adverse affects reported.

Follow-up is not necessary if symptoms resolve, and partner treatment is not indicated. There is no good evidence that probiotic (either oral or intravaginal) administration provides any benefit for treatment or prevention of VVC. Prevention involves education of patients and reduction in any risk factors present: avoiding douching, improved control of serum glucose levels, compliance with treatment regimens, and minimizing the use of antibiotics.

Trichomoniasis

The third most common cause of vaginitis is caused by the flagellated single-celled anaerobic protozoan *Trichomonas vaginalis*. The organism primarily infects the squamous epithelium of the urogenital tract including the vagina, urethra and paraurethral glands, cervix, bladder, Bartholin glands, and prostate. The disease is sexually transmitted though not reportable, and women can acquire the disease from other women though men usually do not transmit it to other men. The incubation period is unknown, but in vitro studies indicate 4–28 days in about 50 % of patients, and it can persist for months in epithelial crypts and periglandular areas of women [10].

Since this disease is not reportable, the prevalence is hard to determine, but the best evidence shows an approximate rate of 3 % in the general population of women [11]. This of course varies according to the population studied and the method of diagnosis. Many women can be asymptomatic carriers (often eventually developing symptoms), but the typical vaginitis presentation is that of a thin, frothy gray or yellow-green vaginal discharge with pruritus and vaginal irritation with burning. The discharge may have an odor, and there may be dysuria, urinary frequency, lower abdominal pain, and dyspareunia as a result of involvement of the entire urogenital tract.

Risk factors for trichomoniasis are related to sexual behaviors, such as multiple sex partners, history of an STD, and lack of condom use, as well as related to race and socioeconomic status. It is associated with adverse outcomes in pregnant and nonpregnant patients. In pregnancy trichomoniasis has shown to increase the rates of preterm birth, premature rupture of membranes, and low-birth-weight infants. Other poor outcomes in women include increased shedding of HIV in those infected with HIV, atypical PID, infertility, and post-hysterectomy cellulitis or abscess.

The physical exam can show very few signs or extensive findings including erythema of the vulva and vaginal mucosa; the characteristic thin, frothy, gray or greenish vaginal discharge, possibly malodorous; and petechiae of the vaginal mucosa and cervix may be present, producing the appearance of the "strawberry cervix" on the pelvic speculum exam. The vaginal pH will be elevated and the whiff test can be positive but the diagnosis is actually made based on the laboratory findings. The wet mount will show the presence of the characteristic motile flagellated trichomonad (Fig. 3) with a jerky and spinning motion, best visualized with the high-power lens (40x). The motility is required for the diagnosis so it is imperative to examine the wet mount immediately after preparation as the organism becomes sluggish and dies in 10–20 min after collection. The usually oval protozoan's size is approximately that of the PMNs, and there will typically be a large number of leukocytes present on microscopy. The sensitivity of microscopy is dependent upon the experience of the microscopist and collection technique and is only approximately 60–70 % [12]. Culture is more sensitive than wet mount and is a diagnostic option, particularly in patients with negative or unavailable microscopy, but fixing and staining can change the morphology so is not useful. The use of nucleic acid amplification

tests (NAAT) is the most sensitive and specific and can be performed on a self- or clinician-collected vaginal swab or utilizing urine or liquid cytology specimen. These DNA tests allow for testing of other STDs, as is recommended in this circumstance (since risk of one STD raises the risk of having another) but are more expensive and not yet widely available. In addition, the wet mount should be carefully examined to rule out other causes of vaginitis, such as BV and candidiasis.

Treatment of trichomoniasis is recommended for both asymptomatic and symptomatic patients and their sexual partners for relief of symptoms and to reduce carriage prevalence and the poor outcomes noted above [5]. Treatment regimens include only oral medications: metronidazole (Flagyl) or tinidazole (Tindamax) 2 g in a single dose, with an alternate regimen of metronidazole 500 mg twice daily for 7 days. These medications have a high cure rate (90 %), and the intravaginal metronidazole gel is less effective, so it is not recommended. In the case of allergy, there are no other medications shown to have the effectiveness of the oral nitroimidazoles so the CDC recommends a desensitization protocol. Partners should be treated simultaneously (if possible) and patients advised to avoid intercourse until completion of treatment in both partners with resolution of symptoms or in the case of asymptomatic patients, 7 days. Side effects are dose dependent and include nausea and/or vomiting, metallic taste, headache, dizziness, and a disulfiram-like reaction, so alcohol consumption should be avoided for about 24 h after metronidazole and 72 h after tinidazole treatment.

Treatment in pregnant patients has not been shown to decrease the rates of adverse outcomes, and there have been some studies that have indicated an increase risk [5]. For this reason treatment of pregnant patients is recommended, but the treatment of asymptomatic patients is not straightforward: counseling them on their risks and benefits of treatment and offering delay of treatment until 37 weeks can decrease perinatal transmission without putting them at increased risk. Partner treatment can be accomplished at any time, with the consistent use of condoms or avoidance of intercourse to decrease reinfection. Metronidazole 2 g in a single dose is the drug of choice as there is insufficient evidence of the safety of tinidazole in pregnancy. In this population who often has increased nausea and vomiting during pregnancy, the multidose regimen of 500 mg twice daily for 7 days can be used as an alternate regimen. In breast-feeding patients, the 2 g dose of metronidazole is relatively high for the neonate so advise patients to suspend breast-feeding (pump and discard) for 12–24 h after the dose can eliminate this factor (72 h if tinidazole is used).

Patients positive for HIV can have increased shedding of the virus with infection with *Trichomonas vaginalis* and treatment can decrease this shedding. Routine screening of asymptomatic patients in this population is recommended at entry into care and at least annually, as well as 3 months after treatment even if symptoms have resolved [5]. Some evidence has shown more effectiveness with the longer multidose regimen of metronidazole.

Follow-up is not recommended if symptoms have resolved, and routine screening has not been shown to be of benefit. Resistance levels to metronidazole have been found to be low, so in the case of recurrences or persistence of symptoms, explore compliance with treatment in both the patient and her sexual partners as this is thought to be the most common contributing factor. If the 2 g metronidazole dose fails, the use of the 500 mg metronidazole twice daily for 7 days or the tinidazole 2 g single dose is recommended. If this regimen fails, the use of either metronidazole or tinidazole 2 g daily for 5 days is recommended. If continued failure occurs after these regimens, consultation with a specialist is recommended to include sensitivity testing of *T. vaginalis* to both metronidazole and tinidazole.

Prevention is managed with patient and partner treatment as well as patient education regarding the frequency of asymptomatic infections, the sexual nature of transmission, an increased risk for HIV acquisition and transmission, and the importance of both patient and partner compliance with prescription treatment regimens. A discussion regarding changing sexual behaviors through the consistent use of condoms or

abstinence, maintaining a mutually monogamous relationship with a noninfected partner, or limiting the number of sexual partners is indicated.

Cervicitis

Inflammation of the uterine cervix can be effected by many of the already noted conditions and can be due to infectious or noninfectious etiologies, with acute typically the former and chronic the latter. The most common infectious etiologies are the STDs chlamydia, *Neisseria gonorrheae*, as well as herpes simplex viruses, *Trichomonas vaginalis*, and BV (discussed elsewhere). Noninfectious causes can be from mechanical or chemical irritation, radiation therapy, and systemic inflammatory diseases. A significant proportion of patients are asymptomatic and detected incidentally on exam, but when present symptoms typically can include varying degrees of vaginal discharge, postcoital bleeding, dysuria, urinary frequency, dyspareunia, or vulvovaginal irritation. The appearance of the cervix on exam will vary depending on the severity and etiology and can include mucopurulent cervical discharge, cervical friability, vesicular or ulcerative lesions, punctuate hemorrhages of the "strawberry cervix," and cervical motion tenderness with palpation. Treatment is directed at the offending etiology and relief of symptoms. When an etiology cannot be found, there is no recommendation for treatment beyond empiric coverage for STDs, particularly in those patients at high risk. Histologic or cytologic cervicitis in asymptomatic women does not require treatment as it is a very nonspecific finding.

Other STDs: GC, Chlamydia, HPV, Pediculosis, HSV, and Syphilis

There is considerable overlap of the symptoms of these conditions and other STDs, and for this reason, all STDs should be entertained when evaluating patients with vulvovaginal complaints and coinfection may be present. STDs are covered in detail elsewhere in this text but a brief description is given here of some of the similar common presentations. The presentation of vulvovaginitis in herpes simplex virus types 1 and 2 can vary widely based on a number of factors but can have the signs and symptoms of vulvovaginal inflammation with edema, pruritus, dysuria, dyspareunia, local pain and itching, and even vaginal discharge. Typically there are characteristic ulcers present on the labia, vagina, and/or cervix to indicate the etiology. Gonorrhea and chlamydia, if symptomatic, typically appear as mucopurulent cervicitis that when wiped away quickly reappears. HPV is discussed later with genital warts. Pediculosis pubis (pubic lice) typically presents with vulvar pruritus, and lice or nits in the pubic hair will be observed on the exam of the genitals. Primary syphilis can present with painful ulcers and secondary syphilis with condyloma lata: flat, moist papules on plaques that can be white, pink, or yellow and can mimic genital warts.

Atrophic Vaginitis

Atrophic vaginitis is an alteration of the normal premenopausal vaginal biological and chemical environment and inflammation that occurs in the mucous membranes of the female genitalia due to the lack of or decreased levels of estrogen. This often occurs in menopausal women but can also occur during other hypoestrogenic states such as postpartum and lactation and when taking antiestrogenic medications. The lack of estrogen stimulation of the cells of the female genital tract results in less glycogen and thinning of the epithelial cells. The decrease in glycogen then results in the loss of lactobacilli with a resultant decrease in lactic acid and hydrogen peroxide, raising the vaginal pH (>5), thus altering the normal premenopausal flora, and making the likelihood of overgrowth or invasion of pathogenic organisms more likely.

Atrophic changes seen as a result of this process include loss of elasticity and thinning of the vaginal epithelium with shortening and narrowing of the vaginal canal and introitus with loss of rugae as well as decreased vaginal secretions.

Together, these make the area more susceptible to even minor trauma producing bleeding, petechiae, and even ulceration. There are estrogen receptors in the structures of the urinary tract derived from the same embryologic origin, including the bladder, urethra, and pelvic floor musculature, that are affected by this same hypoestrogenic state and produce the symptoms of dysuria, urinary frequency, and hematuria. Abstinence can exacerbate the conditions and sexual activity can actually help to preserve the vaginal epithelium and reduce these symptoms by encouraging increased vaginal blood flow and elasticity [13].

The clinical presentation is varying degrees of vaginal dryness, with burning or irritation, sometimes a yellow malodorous vaginal discharge, dyspareunia, dysuria, and urinary frequency and even vulvar or vaginal bleeding and hematuria (not necessarily related to intercourse). The pelvic exam will show the effects of the hypoestrogenic state with sparse pubic hair, decreased vaginal secretions, introital narrowing, fusion or resorption of the labia minora, and pale, dry vaginal epithelium that appears smooth and even shiny with a loss of rugae. There is loss of labial fat that can make the clitoris or urethral meatus look more prominent or even cause urethral prolapse. The vagina can be shortened, narrowed, and poorly distensible. In fact, in severe cases, the cervix can become nearly flush with the vaginal walls as the fornices are obliterated. The vaginal and cervical tissues may show inflammation, have more prominent blood vessels visible through the thinned epithelial tissue, and can show patchy erythema, petechiae, or ulcers with friability of the cervix and easy bleeding of other structures, and there may be a yellow, malodorous discharge present.

The diagnosis is made based on the clinical findings, though laboratory testing is performed in order to rule out any other coexisting conditions. Measuring serum estrogen levels is not usually necessary or beneficial unless there are questionable findings. The laboratory evaluation will show an elevated pH (>5) and lack of lactobacilli on wet mount with a predominance of parabasal cells and may show many PMNs and the presence of other mixed flora. BV and trichomoniasis should be ruled out by the lack of clue cells or motile trichomonads. Parabasal cells are immature squamous epithelial cells that are rounded with a large nucleus to cytoplasm ratio. The maturation index quantifies the proportions of the types of epithelial cells based on their maturity. The superficial and intermediate epithelial cells dominate the wet mount in premenopausal women, whereas in post menopause, there is an increase in parabasal cells, even to the point that no other types are seen.

First-line treatment of atrophic vaginitis is the use of vaginal lubricants and moisturizing agents. The vaginal moisturizing agents should be used on a regular basis, at least one to two times weekly. And water-soluble lubricants should be used generously during intercourse to decrease discomfort. Though these agents do not reverse the atrophic changes, they can be quite useful, particularly in cases of only mild symptoms. Mechanical measures with intercourse itself, dildos, or mechanical vaginal dilators can be used (with lubrication) by a partner or the patient herself to stretch the vaginal tissue, though little is known about the ideal type and frequency that results in the best outcomes.

For moderate to severe symptoms of atrophic vaginitis, local vaginal estrogen therapy is more effective and actually reverses the changes seen by the lack of serum estrogen [14]. The doses used for this condition (7.5–25 mcg weekly) are lower than that used for control of the vasomotor symptoms of menopause and avoid or minimize the systemic estrogenic effects of increased risk for breast cancer and thrombosis as there is little systemic absorption [15]. Local vaginal estrogen is often more effective in treating the vulvovaginal symptoms of atrophy than oral estrogen therapy. In the USA, these agents are available as conjugated estrogen creams and estradiol in the form of cream (though there is increased systemic absorption), tablet, or ring and appear to be equally effective in relieving symptoms, though the dose and duration to achieve this affect can vary across patients. With all of these forms, the typical dosing regimen is to use daily for the first 2 weeks and then decrease to approximately twice weekly or the dose that is effective in controlling symptoms.

In women with an intact uterus, consideration should be given to adding progesterone, either cyclical or continuous, to decrease the risk of endometrial malignancy, though the very low doses used do not appear to stimulate the endometrium [15].

Selective estrogen receptor modulators (SERMs) can be used in this setting and are approved to treat the symptoms of vulvovaginal atrophy [16]. This medication selectively binds to estrogen receptors acting as an estrogen agonist, inducing changes in the vaginal epithelium and decreasing the vaginal pH, and appears to have no detrimental effects on endometrial tissue. This is a daily systemic medication, and side effects are more common than with topical meds, the most common being hot flashes.

There is insufficient evidence to support the use of alternative or complimentary therapies such as oral or vaginal vitamin D or E. The safety of hormonal use in women either at high risk or with a history of breast cancer or thromboembolism has not yet been established, so these therapies are not recommended for these populations.

Vulvodynia

Vulvodynia is vulvar discomfort (typically burning or pain) of unknown etiology with no visible findings or other medical explanation; therefore, it is a diagnosis of exclusion. Vestibulitis is no longer used to describe this condition, as it implies the presence of inflammation which is not part of the condition [17]. The presentation is that of provoked (with penetration or pressure to the vulva) or unprovoked burning or discomfort of the vulva or particular areas of the vulva (clitoris, vestibule), infrequently with pruritus. The physical exam reveals normal or mild inflammatory changes with hyperalgesia of this area; pain with separation of the labia is common. The pathogenesis is unknown and can vary for each individual, but is most likely a combination of factors, including changes in estrogen concentrations, neuropathic pain, pelvic floor dysfunction, and psychological factors [18]. These factors are then thought to precipitate the mind-brain-body cycle seen in other chronic pain syndromes.

There is paucity of data available, and there is no agreement in diagnosis and treatment strategies [18]. Avoidance of any products (dyes, perfumes, other chemicals) or behaviors (use of tight-fitting clothing, horseback or bike riding, daily use of sanitary pads) that can irritate the area is recommended as well as avoidance of constipation. Use of the application of ice packs wrapped in a soft cloth periodically throughout the day or sitz baths in warm water 10–15 min with subsequent application of a thin layer of petrolatum gel can offer some relief. Pelvic floor rehabilitation or physical therapy by those experienced in this disorder has been utilized. Important is addressing the psychosocial and sexual issues with couples and/or sexual therapy, including cognitive behavioral and mindfulness therapy.

Pharmacologic therapy utilizes medications often used in other types of neuropathic and chronic pain: topical lidocaine, tricyclic antidepressants (desipramine, nortriptyline, amitriptyline), gabapentin, pregabalin, venlafaxine, duloxetine, and estrogen cream. Nerve blocks may be beneficial and require referral to either an anesthesiologist or pain specialist.

Allergens and Irritants

Allergic reactions or inflammation of the vulvovaginal area can occur as a result of exposure to various substances, such as spermicides, soaps, deodorants, detergents, dyes, perfumes, pads or panty liners, latex, douching agents, urine, and more chemicals. There can also be mechanical irritation caused by foreign bodies (dildos/vibrators/personal massagers) particularly if prolonged exposure, as in the case of a retained tampon. Symptoms can include pruritus, stinging, soreness, burning, or even a vaginal discharge. It is important to specifically ask patients regarding the use of any feminine hygiene or other products and the frequency as excessive washing can cause dryness and irritation. Exam will reveal local inflammation and possibly excoriation and often discharge and odor in the case of a retained

foreign body. Contact dermatitis can be seen on the vulva with the typical findings of erythematous maculopapular rash. Coinfection can be present so complete exam including microscopy is warranted. Treatment is avoidance of the offending agents and, in the case of a retained foreign body, removal and treatment of any coinfection (routine use of antibiotics in this setting is not necessary).

Dermatoses

There are a number of generalized skin conditions that can include vulvar symptoms ranging from mild to severe, though these uncommonly affect only the vulva. The symptoms, if present, are typically pruritus and/or irritation/soreness. The exam will often reveal the characteristic findings of the respective conditions: seborrheic dermatitis with pink macular area with scale; atopic or contact dermatitis with erythematous papules; molluscum contagiosum with small pearly, umbilicated papules; folliculitis with inflammation and/or infection of the hair follicles; skin tags that are flesh colored or pigmented and usually pedunculated; and lichen simplex chronicus with thickening or lichenification of the skin. The area may show the results of either acute or chronic changes of redness, excoriations, or even fissures. Aphthous ulcers can present on the mucous membranes of the genital area and are similar to the much more common oral form. Treatment would be directed at the particular skin condition in question, covered elsewhere in this text.

Generalized skin conditions can present with primary genital lesions or can present with a different appearance in the genital area, often related to the presence on mucous membranes and the presence of more moisture. Psoriasis affects the genitals in approx 30–40 % of patients with the disease [19]. On the mucous membranes of the vulva, the lesions tend to have less scale, may appear red, and even have exudate present. Typically the lesions do not involve the vagina, and in some cases, the genitals can be the sole presenting location. Tinea can involve the groin and vulva showing sharply marginated, erythematous dusky red, moist plaques or patches with slight scaling and often with satellite lesions and pustules present. When found in the groin, it is termed tinea cruris. Hidradenitis suppurativa when involving the vulva is typically found in the inguinal and labiocrural folds, mons pubis, and perianal area. Typically there are old scars from previous lesions, and frequently edema is present.

Lichen sclerosis is a primary skin condition of unknown etiology that can occur in genital and extragenital locations. Initially the symptoms can be very subjective with itching, dyspareunia, and dysuria, though the typical presentation is that of pruritus, with the appearance of white papules that coalesce into white plaques: the skin becomes thin and slightly wrinkled ("cigarette paper"). On the vulva it can lead to obliteration or alteration of the normal architecture of the labia minora and stenosis of the introitus or can appear as a figure 8 pattern when involving the perineum and perianal areas. There is an increase in the risk of squamous cell carcinoma so biopsy may be indicated for any suspicious lesion or failure to respond to therapy.

Lichen planus also has an unknown etiology involving the mucocutaneous areas of the body and often has simultaneous oral and genital presentations. Lesions can be papulosquamous with flat white plaques or erosive with red or violaceous, sharply marginated, flat-topped papules or plaques with a thin white lacy network of white or gray lines usually on the labia minora and introitus (sometimes on the vaginal wall). Papulosquamous may be asymptomatic or with some pruritus, whereas erosive are often painful and can even have bleeding.

Fistulas and Crohn's Disease

Rectovaginal, anovaginal, and less commonly vesicovaginal fistulas can cause symptoms of vulvovaginitis, including malodorous vaginal discharge, pruritus, inflammation, and dyspareunia. In some cases stool or gas is passed from the vagina, making the diagnosis much easier. Often these lesions are palpable on rectal exam, usually located in the midline, lower third of the vagina, along the posterior vaginal wall, and on vaginal

exam may be just inside the introitus or hymen. On exam the appearance is that of a red velvety, indurated area. Fistulas can result as a complication of pelvic surgery, vaginal delivery, radiation therapy, more rarely spontaneously, or due to other pathologies such as inflammatory bowel disease. Crohn's disease can also be present on the vulva as knifelike linear ulcers, particularly in the skin folds. Initial presentation can be only vulvar edema or abscesses that break down to form chronic ulcers (which can mimic hidradenitis suppurativa) and/or large vulvar skin tags.

Bartholin Glands and Duct Disorders

Bartholin glands are mucous-secreting glands that begin functioning to provide moisture to the vestibule of the perineum at puberty and typically involute with age, particularly with menopause. They are small (approximately 0.5 cm) and are connected to the vestibule with a short duct (approx 2–2.5 cm) that opens at the 4 and 8 o'clock positions on either side of the vaginal orifice between the hymenal ring and labia. Cysts and abscesses are formed when there is obstruction of the opening of the duct, with resultant accumulation of the mucous secretions proximal to the obstruction, or cystic dilation of the duct and can become infected (though abscesses can occur without the formation of a cyst). They should be differentiated from other masses found on the vulva and perineum such as lipomas, folliculitis, hidradenitis suppurativa, sebaceous cysts, hematomas, Skene gland cysts (located more anteriorly on either side of urethral openings), other vulvar abscesses, hernias, or even extensions of perianal abscesses.

Both cysts and abscesses are typically unilateral and found in the area of the Bartholin gland and should not be fixed to any underlying tissues: this can be suspicious for malignancy. The cysts are typically smaller than abscesses (approx 1–3 cm) and may be asymptomatic though if large can cause some discomfort. Abscesses, which are more common, are typically larger and quite painful, often to the point the patient is barely able to sit or ambulate normally. On clinical exam cysts are usually soft and non-tender, whereas abscesses are soft, painful masses that protrude into the posterior vaginal introitus and often extend into the labia. There can be associated cellulitis with increased warmth, erythema, fluctuance, induration, and edema. The presence of any palpable solid or irregular mass can be an indication of the presence of malignancy, though this is rare, particularly in premenopausal women. If there is any suspicion of malignancy in postmenopausal women with their first occurrence, biopsy should be obtained [20].

Cysts may require no management, unless large and uncomfortable. Abscesses should be treated at the least with incision and drainage (I&D), though some may spontaneously rupture and drain. The risk of recurrence due to healing of the edges of the incision and reaccumulation of the gland secretions is quite high [21], so further management is recommended with either placement of a Word catheter, marsupialization, silver nitrate stick ablation, laser vaporization, or complete excision. I&D involves sterile prep of the area, administration of a local anesthetic with an incision into the protruding mass in the area of the duct opening external to the hymenal ring to drain the contents. Irrigation and hemostats can be used to break up any loculations present within the cyst or abscess. With all of these procedures, there is a risk of labial or perineal edema, hematoma formation, bleeding, cellulitis, scarring, and dyspareunia.

Antibiotics are typically not necessary unless there is accompanying cellulitis or high risk for complicated infection such as recurrence, immunocompromised patients, pregnancy, risk for MRSA, systemic signs of infection, or suspicion of gonorrhea or chlamydia infection. The infection is typically polymicrobial with the most common aerobic pathogens of staph, strep, and E coli and anaerobic bacteroides with sexually transmitted infections (such as gonorrhea, chlamydia, and trichomonads) decreasing in incidence [22]. When indicated, empiric treatment is started before results of any cultures are received and includes amoxicillin-clavulanate (Augmentin) 875 mg BID to cover E coli and strep, with

clindamycin (Cleocin) 300 mg four times a day for staph and bacteroides, both for 7 days. If culture results reveal an STD, it should be treated accordingly.

Word catheter placement involves the placement of a small (stem is approximately 1 in. and diameter is similar to that of a 10 French Foley catheter) balloon-tipped catheter into the incision immediately after the performance of I&D, with inflation of the balloon with 2–3 cm^3 of saline in order to keep it in place and the end tucked into the vagina. If the incision is too large, the catheter will fall out, so it is recommended only about 5 mm incision in this case. The catheter is left in 4–6 weeks to allow epithelialization of a new tract for drainage of the gland secretions; therefore, it is important to ensure the tip is placed within the cyst wall so as to avoid the development of a false tract. At this time the balloon can be deflated and the catheter removed without anesthesia. This procedure is easily accomplished in the office with local anesthesia and is relatively quick and easy, though the patient may experience post-procedure discomfort or the catheter can migrate or become dislodged and fall out before epithelialization, increasing the risk for recurrence. Daily sitz baths after the procedure can help with discomfort.

Marsupialization involves a larger incision over the cyst or abscess or even an excision of an ellipse of the roof of the mass, with the length dependent on the size of the cyst (usually 1–3 cm). Drainage is followed by suturing with eversion of the edge of the cyst wall onto the epithelial surface of the vestibule with interrupted absorbable sutures allowing for the formation of a new ductal orifice for drainage of gland secretions. This procedure is as effective as placement of a Word catheter and also can be accomplished easily in the office setting with local anesthesia, though is somewhat more complicated and time consuming [21]. Again, daily sitz baths are typically recommended.

The placement of a silver nitrate stick (approx 0.5 cm in size) deep within the cyst/abscess after I&D can also be done in the office setting with local anesthesia. The wound is then dressed with gauze and the patient instructed to return in 48 h for debridement of the wound of silver nitrate particles and necrotic tissue. This procedure has been found to be as effective as complete excision [21]. There is significantly more post-procedure discomfort than the previous procedures described and risks of chemical burns to nearby tissue, though there is less healing time, expense, and risk than that of complete excision. Carbon dioxide laser ablation can be accomplished with the use of local anesthesia as well and is effective in treating this condition, though it requires expertise and training in the use of very expensive equipment not typically available in the office setting of family medicine. Complete excision of the gland and duct is definitive treatment though it requires surgical excision in the operating room, with all of the increase in cost and risks inherent to these more involved invasive procedures. For these reasons complete excision is usually used only when recurrent disease fails numerous other attempts at treatment, or malignancy is suspected (though biopsy is the first-line approach). The loss of gland function can rarely cause vaginal dryness and dyspareunia.

Genital Warts

Genital warts are one of the clinical manifestations of infection with the sexually transmitted human papillomavirus (HPV), most commonly types 6 and 11 with low oncogenic potential. Transmission is through direct skin contact during sexual activity, so increased risk exists for patients with increased numbers of sexual partners and history of other STDs, including HIV. Those patients infected with HIV are more likely to develop genital warts than those without [23], and the lesions are more recalcitrant to treatment due to the depressed cell-mediated immunity. The infection itself and the warts are asymptomatic, though there can be pruritus, pain, or discomfort in some patients. The lesions appear as flesh colored or pink, flat, papular, or verrucous papilliform growths on the genital mucosa. They commonly occur around the introitus, but can occur in and around the anogenital epithelium including the cervix, vagina, urethra, perineum,

and perianal skin. Large exophytic masses can cause obstruction of the perianal orifices and interfere with urination, defecation, and vaginal delivery.

Diagnosis is usually clinical, based on visual inspection and can be confirmed with biopsy, though not necessary. The application of 5 % acetic acid solution causes the lesion to turn white and can aid in diagnosis, with or without the use of colposcopy. A similar-looking normal variant of vulvar anatomy is vestibular papillomatosis with monomorphous, symmetrical, soft, closely set projections usually the same color as the mucous membrane of the vestibule (or sometimes more red), whereas warts are firmer, flesh colored, cauliflower-like (multiple projections from a single base). The indication for biopsy prior to treatment is to rule out any malignant or premalignant lesions as squamous cell carcinoma can coexist. Biopsy is recommended when the diagnosis is uncertain; lesions do not respond to standard therapy; the disease worsens during therapy; the lesion appears atypical, particularly if pigmented, asymmetrical, or irregular border, fixed, bleeding, or ulcerated; or the patient is immunocompromised. Colposcopy and biopsy are recommended for any cervical exophytic lesions. Testing for HPV type is not indicated as it does not change management strategies.

Treatment is only indicated for the relief of symptoms, including cosmetic or psychological concerns, as it does not eliminate all cells infected with the virus and it is unknown if it reduces risk of transmission. Spontaneous resolution does occur at varying rates reported (approximately 20–40 %), so expectant management is an acceptable option, though the patient should be counseled that the lesions may spontaneously regress, increase in number or size, or remain unchanged over time. No one treatment option has been shown to be superior to others [5], and not one treatment is right for all patients and every type of wart. Choice of treatment is based on location and size of lesions, patient characteristics (pregnant or immunocompromised), available resources, and clinical expertise, as well as patient preference, including side effects, cost, and convenience. Options include patient- or provider-applied solutions for ablative or immune-mediated destruction of the lesions or surgical techniques. Intra-anal lesions should be referred to a specialist for surgical treatment.

Patient-applied regimens require the patient to be able to identify and reach all of the lesions to be treated. These regimens include podofilox (Condylox) 0.5 % solution or gel, applied to the wart with a swab or finger for 3 days and then no treatment for the other 4 days of the week, up to four cycles; imiquimod (Aldara) 5 % cream applied daily before bed and then washed off 6–10 h after application, three times per week up to 16 weeks; and sinecatechins (Veregen) 15 % ointment, apply 0.5 cm strand and spread with the finger into a thin layer covering the wart three times per day (do not wash off) for up to 16 weeks. Provider-applied regimens include cryotherapy with liquid nitrogen or a cryoprobe every 1–2 weeks; podophyllin resin 10–25 % in a compound tincture of benzoin applied and allowed to dry before patient sits, stands, or dresses and washed off 1–4 h later, weekly, with a limit of <0.5 ml or treating a total area <10 cm^2 with no open or ulcerated lesions; and tri- or bichloroacetic acid 80–90 % apply a small amount to only the wart tissue and allow the white frosting to develop with drying before allowing the patient to move (in order to avoid irritation to surrounding areas), weekly. If pain is too severe or an excess amount is applied, the area can be treated with soap or sodium bicarbonate solution. Surgical excision techniques are recommended for those with larger or greater number of lesions and are typically more expensive and invasive, with more risk associated but do have the advantage of removal of the warts in one visit.

Warts can proliferate and become friable in pregnancy and imiquimod, sinecatechins, podophyllin, or podofilox should not be used. Rarely types 6 and 11 can cause respiratory papillomatosis and laryngeal warts in children, though the route of transmission is unknown, and it is not clear if cesarean delivery prevents this risk [5]. Cesarean delivery may be indicated in the case of large exophytic lesions that may

obstruct the birth canal or increase risk of excessive bleeding.

Most lesions respond to treatment within 3 months. A change in treatment modality is indicated if the lesions do not respond to a full course of therapy or if side effects are too severe. Recurrence is common, particularly in the first 3 months after treatment. Complications are less common if treatment is administered properly, but side effects are quite common. Hypo- or hyperpigmentation is common with the ablative and immune-modulating therapies. Depressed or hypertrophic scarring risk is greater if insufficient time is taken for healing between treatments. Rarely disabling chronic pain syndromes (vulvodynia, hyperesthesia), painful defecation, or systemic effects (due to podophyllin resin) can occur. Local irritation with discomfort and inflammation, pruritus, erosions, and blistering are the most common side effects.

There are vaccines available for the prevention of HPV, at least one of which (the quadrivalent) encompasses types 6 and 11 and is currently recommended for both boys and girls at the age of 11–12 and up to age 26 if not already immunized. The best time for vaccination is prior to sexual activity, but can be given even after the presence of HPV has been diagnosed, as it may confer immunity to other types. Other prevention measures include decreasing the number of sexual partners and use of condoms; although correct and consistent use can decrease the risk of HPV infection, since they do not cover all areas of skin contact with sexual activity, they not eliminate the risk.

The diagnosis of any STD can precipitate many questions and concerns about sexual fidelity of either the patient or her partner. There is a social stigma that is associated with genital warts that may discourage patients from initiating these conversations with their family doctor, so offering counseling and initiating this discussion by the clinician can be very beneficial and is advised. Some of the issues particular to genital warts and HPV can be as follows: the types of HPV that cause most genital warts do not cause the other types of anogenital cancers; diagnosis with HPV of one partner in a relationship does not indicate infidelity in either partner as the virus is usually asymptomatic and there is a considerable lag time between the time of infection and the time of wart formation; it is impossible to determine at what point and from whom the patient acquired the HPV; it is not life-threatening and only in rare and unusual cases leads to cancer; it does not affect a woman's fertility or ability to carry a pregnancy to term; the treatments available can eliminate the wart, but not the virus itself; and it is unknown how long a person remains contagious.

Malignancies

Pruritus can be a presenting symptom of vulvar intraepithelial neoplasia (VIN), which can be HPV or non-HPV associated. They can appear as raised white papules or plaques, but can be red, pink brown, or gray. Typically they are asymptomatic and a biopsy of the lesion is recommended to rule out any high-grade lesions. Advanced cervical intraepithelial lesions can present with vaginal discharge and can mimic cervicitis with friability. A serosanguinous vaginal discharge with or without odor can be present with malignancies in the upper genital tract, such as the endometrium and fallopian tubes. In these cases the usual workup with history, physical, and laboratory evaluation above will rule out these common conditions and often suggests an alternate diagnosis.

Social Issues

Approximately 25–40 % of patients with vulvovaginal complaints will have no identifiable cause after the initial office evaluation, including the history and physical and laboratory studies described above. Getting more detail of history including sexual practices, use of hygienic products, and the timing of or associated symptoms or having the patient refrain from any use of products in the genital area and return for another full exam can be helpful. All of these patients should have cultures or NAAT specimens sent for STDs, including trichomoniasis and possibly *Candida* (if the history and exam support this diagnosis) as not all of these cases will be identified with the use of microscopy.

Vulvovaginitis and cervicitis can be a very sensitive subject for many patients not only because of the vulnerable nature of the examination but can bring up many personal relationship issues: How did they get this condition? And from whom? Is their partner to blame or at risk? What did they do to contribute to the acquisition and how can they avoid it in the future? The physician should understand the sensitive nature of these concerns and anticipate these questions or concerns, realizing some patients may be too uncomfortable to raise the questions at the office visit. Explanations should be given regarding the nature of transmission, any contributing factors, and the importance of compliance and partner treatment when applicable. Patients should be discouraged from douching as this alters the vaginal flora and can contribute to the condition and the patient's symptoms. Use of condoms and limiting the number of sexual partners through monogamous long-term relationships can reduce the patient's exposure to and risk of acquiring these types of conditions. Providing written information or resources for the patient to access is very beneficial in directing them to reliable sites for further information.

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Menstrual Disorders

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General Principles

Menstrual Cycle

Women experiencing menstrual disorders frequently call upon family physicians. The disorders are heterogeneous and stem from multiple etiologies, spanning the breadth of many disciplines including genetics, metabolism, endocrinology, gynecology, and psychology. Menstrual disorders are well addressed through a comprehensive primary care approach.

Normal Physiology and Patterns

Regulation of the menstrual cycle is a product of complex, delicate interactions among the hormones of the hypothalamus, pituitary, and ovaries. The hypothalamus secretes gonadotropin-releasing hormone (GnRH) in a pulsatile manner. The pituitary secretes luteinizing hormone (LH) and follicle-stimulating hormone (FSH) that act primarily on the theca and granulosa cells of the ovary respectively. With FSH and estradiol stimulation, a dominant follicle develops and releases an egg. Estradiol has a negative feedback effect on FSH, resulting in decreased stimulation of the several other less mature follicles that develop monthly. The follicular phase of the menstrual cycle, under control primarily of FSH, results in ovulation and lasts 10–14 days. During this phase, estrogen stimulates endometrial proliferation, and progesterone receptors are synthesized on endometrial epithelial cells.

When the concentration of estradiol reaches a threshold level for a specific duration, the LH surge occurs. The LH surge triggers ovulation and formation of the corpus luteum. The luteal phase of the menstrual cycle is the period after the LH surge and consistently lasts 14 days after the mid-cycle surge. The progesterone produced by the corpus luteum causes changes in endometrial glandular secretions and in the endometrial stroma. The corpus luteum produces estrogen and progesterone, which have negative feedback results on GnRH and FSH, eventually leading to decreased levels of estrogen and progesterone and involution of the corpus luteum if pregnancy has not occurred.

In the absence of pregnancy, the regression of the corpus luteum and the drop in progesterone levels result in endometrial sloughing, or menstruation. Subsequently, FSH levels increase to prepare for the next cycle.

Normal menstrual cycle intervals are 21–45 days from the first day of one cycle to the first day of the next, with bleeding lasting 3–7 days. Average blood loss is 30–40 mL per cycle. The average age of menarche in the United States is 12 years and menopause is 52. Figure 1 is a graphic illustration of the interactions of key hormones and their effects on the endometrium and ovary during the menstrual cycle.

Terminology

Inconsistency in terminology of menstrual disorders has interfered with clarity in their evaluation and treatment and hampered research efforts in this field. In 2011, the Federation of International Gynecology and Obstetrics (FIGO) published their recommended terminology for abnormal uterine bleeding [1]. Their schema for abnormal uterine bleeding (AUB) is among the terms defined below, with the

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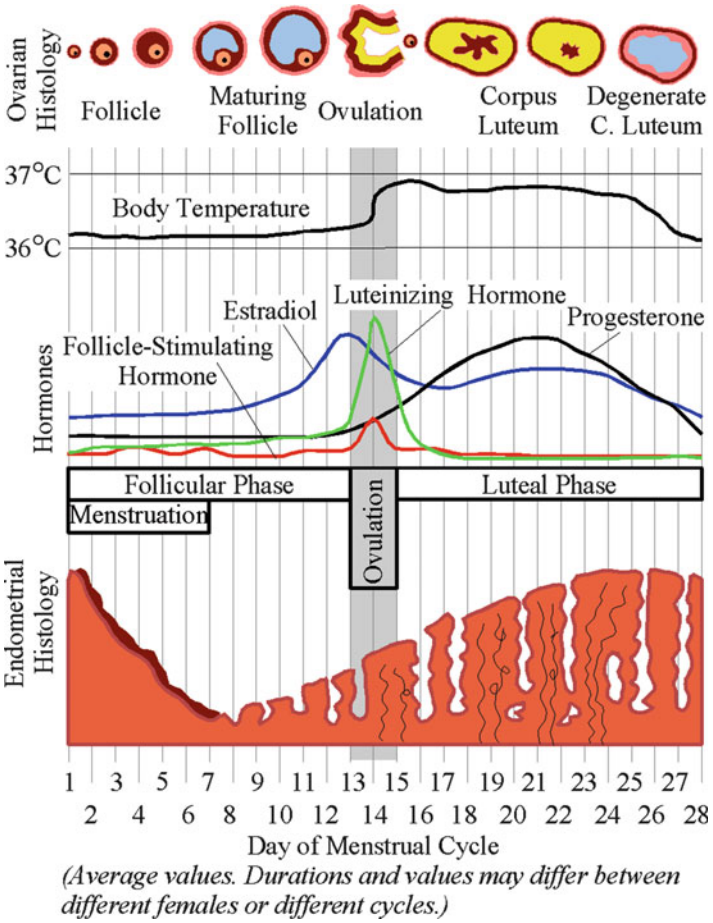

Fig. 1 The menstrual cycle. Chris 73/Wikimedia Commons [GFDL 1.3 (www.gnu.org/licenses/fdl-1.3.html) or CC BY-SA 3.0 (http://creativecommons.org/licenses/by-sa/3.0)], via Wikimedia Commons

recommendation that terminology including menorrhagia, metrorrhagia, and dysfunctional uterine bleeding be discarded in favor of the terms listed under AUB below.

Menarche: onset of first menses

Amenorrhea: absence of menstrual periods

1. Primary amenorrhea: lack of menarche by age 13 in girls without development of secondary sexual characteristics or by age 15 in those with secondary sexual characteristics
2. Secondary amenorrhea: absence of menses for three consecutive cycles in a previously regularly menstruating woman or for 6 months in a woman with oligomenorrhea

Menopause: cessation of menses for 12 months not due to pregnancy or for 6 months in a woman over 50

Abnormal uterine bleeding: bleeding that is abnormal in timing, flow, or duration [1]

- ***Acute AUB***: heavy bleeding of sufficient quantity that immediate intervention is required
- ***Chronic AUB***: abnormal in volume, regularity, and/or timing and has been present for the majority of the past 6 months and does not require immediate intervention
- ***Intermenstrual AUB***: occurs between clearly defined cyclic and predictable menses

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- ***Heavy menstrual bleeding***: characterized by blood loss of greater than 80 mL in a cycle or passing large clots or soaking through pads or tampons within an hour and associated with anemia

Approach to Patient

Any woman presenting with a menstrual disorder should have a thorough and pertinent history and physical examination. The key components of the history are a menstrual, reproductive, and contraceptive history; a general medical history including medications used; and nutritional, exercise, and emotional assessments. A family medical history and history of reproductive or menstrual disorders should also be obtained. The elements of history taking for menstrual disorders are outlined in Table 1.

The focus of the physical examination is on identifying abnormal anatomy such as an imperforate hymen or an enlarged fibroid uterus and assessment for androgen excess, estrogen deficiency, or an endocrinopathy. Elements of a focused physical examination are outlined in Table 2. Laboratory and imaging studies are often required elements of evaluation. They are listed in Table 3 and are discussed under each condition.

Amenorrhea

Primary Amenorrhea

Congenital anomalies are the main cause of primary amenorrhea. These include imperforate hymen or a vaginal septum that will be detected on exam and can be treated surgically. Congenital absence of the uterus and vagina can occur. Androgen insensitivity leads to a 46,XY female who has no uterus or tubes and a blind vaginal pouch. Testes are found within the abdomen or inguinal hernias and require surgical removal due to risk of malignant transformation. Women with Turner's syndrome, 46,XO, never menstruate because ovaries do not develop. Patients with congenital anomalies require specialty consultation. Women with primary amenorrhea and normal sexual development should undergo the same evaluation as patients with secondary amenorrhea.

Secondary Amenorrhea

History and physical examination may point to specific causes of secondary amenorrhea, including the presence of chronic conditions or medications that can alter menstrual patterns. Laboratory evaluation always begins with the pregnancy test. If this is negative, obtaining a thyroid-stimulating hormone (TSH), prolactin level, and FSH and LH will help identify thyroid disorders, hyperprolactinemia, primary ovarian insufficiency, and menopause as the cause for amenorrhea. Primary ovarian insufficiency refers to ovarian follicle depletion or dysfunction prior to age 40. Hyperprolactinemia may be due to benign tumor of the pituitary gland or to medications such as OCPs, tricyclic antidepressants, opiates, antihypertensives, and antipsychotics [2]. If the prolactin level is greater than 200 ng/mL, magnetic resonance imaging (MRI) is recommended to evaluate for a pituitary tumor. If all the tests are normal, consider additional evaluation for evidence of disordered eating, excessive exercise, and poor nutritional status leading to functional hypothalamic amenorrhea. If there is evidence of hyperandrogenism, evaluate further with serum testosterone and 17-hydroxyprogesterone to differentiate among polycystic ovary syndrome (PCOS), late-onset congenital adrenal hyperplasia, or an ovarian or adrenal tumor producing androgens [3]. Elevated levels of LH and FSH make the diagnosis of ovarian failure. If LH is elevated and FSH is normal, further testing can be done for congenital adrenal hyperplasia (17-hydroxyprogesterone), Cushing's syndrome (cortisol levels), and ovarian or adrenal malignancies (testosterone level). If those tests are done, with normal 17-hydroxyprogesterone and cortisol and moderately elevated testosterone, polycystic

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Table 1 Elements of history taking

Menstrual history	Age at menarche
	Usual menstrual pattern
	Cycle length (normal 21–35 days)
	Duration (normal 1–7 days)
	Flow (normal < 1 pad or tampon per 3 h)
	First day of last period
	Moliminal symptoms (breast tenderness, mittelsmerz)
	Dysmenorrhea
Gynecologic and sexual history	Use of contraception
	Pregnancies, deliveries, complications
	Pelvic procedures (e.g., dilation and curettage)
	Pelvic pain
Family history	Age of onset of menarche and menopause in sister(s) and mother
	Similar menstrual dysfunction in others
	Congenital syndromes or anomalies
	Endocrine disorders
General medical history	Changes in weight
	Emotional stressors
	Exercise habits and related disorders such as stress fractures
	Sexually transmitted diseases
	Medications
	Chemotherapy or radiation
	Endocrine or metabolic disorders, particularly diabetes or thyroid disorders
	Disordered eating
	Trauma
	Galactorrhea
Screening for disorder of hemostasis [1]	Heavy menstrual bleeding since menarche
	Postpartum hemorrhage, surgical–related bleeding or bleeding associated with dental work
	Two or more of the following:
	Bruising one to two times monthly
	Epistaxis one to two times monthly
	Frequent gum bleeding
	Family history of bleeding symptoms

ovary syndrome (PCOS) is the likely diagnosis; this condition is described separately below. Highly elevated testosterone levels suggest malignancy of the ovary or adrenal gland [2]. Low levels of LH and FSH may be caused by pituitary failure as well as by hyperprolactinemia. An algorithm for the laboratory evaluation of secondary amenorrhea that minimizes diagnostic error while considering costs by obtaining tests in stepwise fashion is presented as Fig. 2; the authors used a definition of no menses for 6 months in a previously regularly menstruating woman or for 12 months in a woman with irregular menses [2]. The same evaluation may be undertaken after 3 and 6 months respectively to help identify causes and provide treatment in a more timely fashion.

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Table 2 Elements of physical examination

General	Height and weight
Skin	Acne, alopecia, hirsutism, abdominal striae, pallor
Neurologic	Visual field deficit
Neck	Thyroid nodules or enlargement
Breasts	Tanner stage, galactorrhea
Abdomen	Adrenal mass
External genitalia and vagina	Imperforate hymen, vaginal septum, atrophic vaginal mucosa, scant cervical mucus, enlarged clitoris
Cervix	Friability, inflammation, polyps, duplication
Uterus and ovaries	Enlargement of uterus and ovaries

Table 3 Laboratory and imaging evaluation

Test	Condition	Menstrual disorder
Pregnancy test	Positive in pregnancy	Amenorrhea, AUB
Thyroid stimulating hormone (TSH)	Hyper or hypothyroidism	Amenorrhea, AUB, HMB
Prolactin (PRL)	Elevated in hyperprolactinemia due to medication or adenoma	Amenorrhea, AUB
LH	Slight elevation common in PCOS, CAH, Cushing's disease	Amenorrhea, AUB
	Decrease in pituitary failure or elevated PRL	
FSH	Elevated in menopause or primary ovarian failure	Amenorrhea, AUB
	Low in pituitary failure or elevated PRL	
Testosterone	Mildly elevated in PCOS	Amenorrhea, AUB, virilization
	Very elevated in androgen producing tumor in ovary or adrenal	
17-hydroxyprogesterone	Congenital adrenal hyperplasia	Amenorrha, AUB
Cortisol	Cushing disease	Amenorrhea, AUB
CBC	Anemia, platelet count	AUB, HMB
PTT, INR	Disorders of hemostasis	AUB, HMB
Ristocetin cofactor, coagulation factors	Disorders of hemostasis, based on abnormal history screen or labs	AUB, HMB, with positvie screen for hemostasis disorder
Cervical, vaginal culture	Endometritis, cervicitis	AUB, dysmenorrhea
Endometrial biopsy	Endometrial hyperplasia or cancer	AUB
Transvaginal ultrasound	Endometrial hyperplasia, cancer, leiomyomas, possibly polyps or adenomyosis, endometriosis	AUB, dysmenorrhea
Saline infused sonohysterogram	As above, more likely to detect polyps or discrete intracavitary abnormalities	AUB
Hysteroscopy	As above	AUB
Laparoscopy	Endometriosis	Dysmenorrhea
MRI pituitary	Pituitary adenoma	Amenorrhea, AUB
MRI pelvis	Adenomyosis, leiomyomas, endometriosis	AUB, dysmenorrhea

Female Athlete Triad

The female athlete triad, one feature of which is amenorrhea, warrants special note because of its common presentation to primary care physicians and its potential consequences. Osteoporosis and disordered eating are the other two aspects of the triad. In this condition, vigorous athletic training and weight

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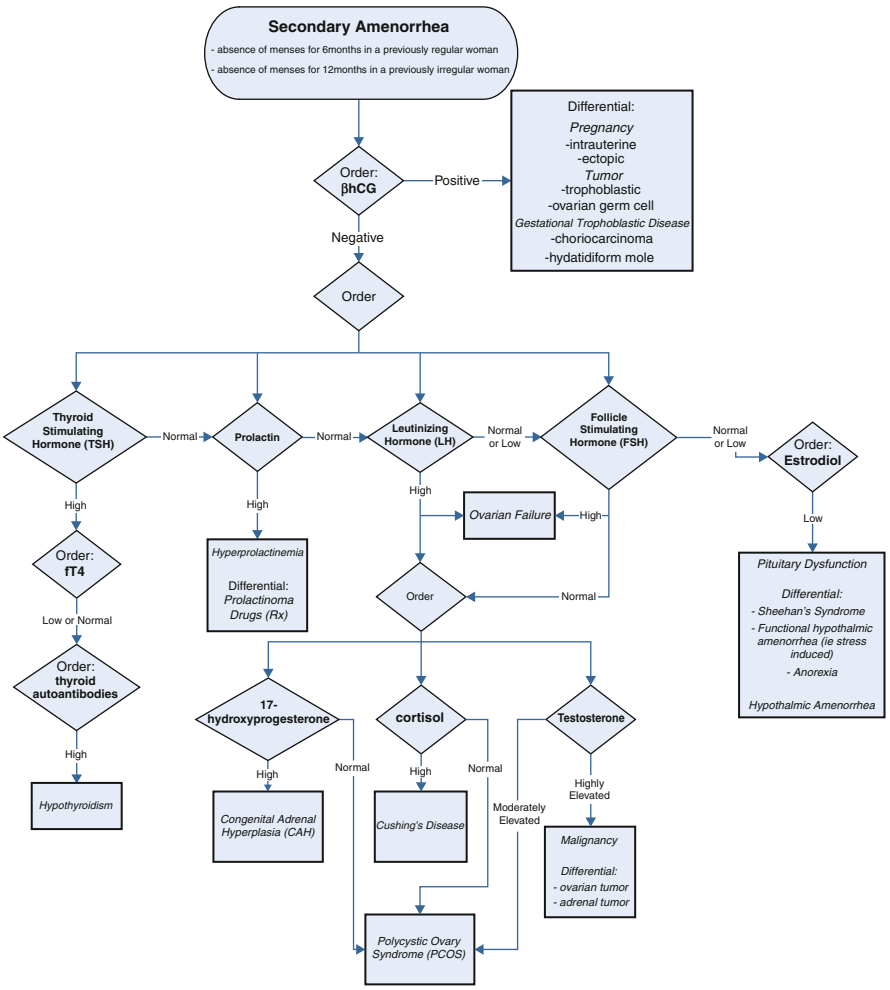

Fig. 2 Algorithm for laboratory evaluation of secondary amenorrhea (Used with permission Roberts-Wilson et al. [2])

changes result in low energy availability, producing hypothalamic dysfunction and either primary or secondary amenorrhea. The associated low estrogen levels lead to osteoporosis. Osteoporosis is especially devastating if it occurs in adolescence when bone density should be peaking. Stress fractures and other fractures due to osteoporosis may be the presenting problems in athletes. The disordered eating associated with the female athlete triad may not meet the strict definitions of anorexia nervosa or bulimia but is prevalent among female athletes. Physicians should review exercise and eating habits with all women presenting with amenorrhea or fractures. Evaluation, as outlined above for secondary amenorrhea, should take place for those young women who have missed three menstrual periods. If no other cause is found, treatment of the eating disorder through counseling, nutritional advice, and possibly medications and a change in exercise patterns will usually result in resumption of menses. Important adjuncts to treatment of the female athlete triad include preventive measures for osteoporosis including ensuring adequate intake of calcium and vitamin D.

Abnormal Uterine Bleeding

Terminology related to abnormal bleeding patterns has been inconsistent. In 2011, the Federation of Gynecology and Obstetrics (FIGO) published recommendations from a panel convened to "develop an agreed pragmatic classification system with a standardized nomenclature to be used worldwide by researchers and clinicians investigating and treating women of reproductive age with AUB" [1]. The

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FIGO schema divides causes of AUB into structural and nonstructural causes, with nine main categories, which are arranged according to the acronym PALM-COEIN:

"Structural" causes = "PALM"
- **P**olyp – endometrial or endocervical
- **A**denomyosis – endometrial tissue within the myometrium
- **L**eiomyoma – submucosal or other
- **M**alignancy and hyperplasia

Nonstructural causes = "COEIN"
- **C**oagulopathy – including chronic anticoagulation (placed here rather than iatrogenic)
- **O**vulatory dysfunction – most often PCOS, hypothyroidism, hyperprolactinemia, stress, obesity, anorexia, weight loss, or extreme exercise or due to medications; also often occurring at extremes of reproductive age: adolescence or perimenopause
- **E**ndometrial – due to a primary disorder of the endometrium, e.g., deficiencies in vasoconstrictor production or inflammation or infection
- **I**atrogenic – including hormonal contraceptives; medications that impact ovulation including tricyclic antidepressants, phenothiazines, and serotonin reuptake inhibitors
- **N**ot yet classified

Evaluation and Treatment of AUB

Women may have more than one factor contributing to AUB and may have conditions that are present but not contributory. Evaluation of AUB begins with the history and physical exam. The patient's age may point toward the anovulation common around menarche or close to menopause. Other historical features listed in Table 1 will help guide the evaluation toward etiologies including infection, tumors, endocrinopathies, medication effects, and disorders of hemostasis. Presence of risk factors for endometrial cancer including hypertension, diabetes, family history, obesity, early menarche, late menopause, or periods of unopposed estrogen should heighten concern for cancer. The general appearance of a patient with AUB may direct the physician toward PCOS or the female athlete triad as causes for irregular bleeding. Some structural causes may be easily discernible on physical exam such as cervical polyps or uterine leiomyomas. Table 2 lists pertinent physical findings that may indicate other disorders.

Treatment of AUB is directed at the primary etiology if one can be found. Usually, treatment has two goals: control of bleeding and prevention of endometrial hyperplasia. Treatment may be medical or surgical and depends of degree of symptoms, desirability of pregnancy, and the patient's preferences.

Authors developed a practical approach to AUB based on how clinicians evaluate and treat AUB [4]. The first steps are taking a history and performing a physical exam, confirming that bleeding is from the uterus. A pregnancy test must be done to confirm that bleeding is not pregnancy related. If not, it can be classified in one of the four categories below. These correspond closely to the FIGO terminology in some cases.

1. Severe acute bleeding – Acute AUB
2. Irregular bleeding – often AUB – O
3. Heavy bleeding – AUB – Heavy menstrual bleeding; often AUB – A, AUB – L, AUB-E
4. Bleeding associated with contraceptive methods AUB – I

Severe Acute Bleeding Severe acute bleeding may be the first presentation of a coagulation disorder in an adolescent. Women on anticoagulants and who have submucosal fibroids may also present with severe acute bleeding.

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After history, physical examination, and a pregnancy test, evaluation may include a transvaginal ultrasound, TSH, CBC, INR, and PTT, with further evaluation for platelet function and clotting factor abnormalities if needed.

Treatment must be provided emergently, with patient's stability directing whether this can be done as an outpatient. An expert consensus panel recommended antifibrinolytic agents (tranexamic acid) and intravenous estrogen as first-line treatment options for acute AUB without disorders of hemostasis, along with possible use of balloon tamponade [5]. Oral estrogen can be used in some cases. Once stabilized, women can be treated with a tapering dose of combination OCP over a month followed by use of oral contraceptives for 3 months. If there are contraindications to combination OCP, cyclic progestins can be used for 3 months. Second-line options for severe acute bleeding include dilation and curettage, endometrial ablation, uterine artery embolization, and hysterectomy. For women with bleeding disorders, management of acute AUB is targeted at the underlying disorder.

Irregular Bleeding For women with irregular bleeding, history and physical exam may point to the cause, including inconsistent ovulation around menarche or menopause, severe systemic illness, endometritis, or medications that interfere with ovulation as listed above under AUB-I. The physical exam may point to androgen excess common in PCOS, described in more detail below, or toward the female athlete triad.

After pregnancy is ruled out, a TSH is obtained, with the addition of prolactin level if there is oligomenorrhea. A pelvic ultrasound may confirm or reveal fibroids as a cause of heavy and sometimes irregular vaginal bleeding, and an endometrial lining thickness of less than 5 mm helps to reassure that AUB is not due to endometrial hyperplasia or cancer. Any patient with AUB over age 35 or at increased risk for endometrial cancer due to unopposed estrogen stimulation should have sampling of the endometrium. Endometrial biopsy is 91 % sensitive and 98 % specific for identification of cancer and 82 % sensitive and 98 % specific in diagnosis of hyperplasia with atypia [6]. The endometrial biopsy procures a small sample of the total endometrium; if a biopsy is normal but bleeding persists, it should be further evaluated with direct visualization with transvaginal ultrasound, hysteroscopy, or saline infused sonohysterogram which can help identify intracavitary abnormalities including polyps and adenomyosis and can direct sites for biopsy [7]. In identification of intracavitary abnormalities, the sensitivity and specificity of these tests is as follows: hysteroscopy 94 % and 89 %, saline infused sonohysterogram 88–99 % and 72–95 %, and transvaginal ultrasound 60–92 % and 62–93 % [6].

Treatment depends on patients' goals and values and the cause of the irregular bleeding. If the patient wants to achieve pregnancy, ovulation induction can be done. If the patient does not desire pregnancy, she can be treated with OCPs for 3 months, with levonorgestrel intrauterine system or with cyclic progestins. If abnormal bleeding does not resolve after 3 months of treatment, higher-dose OCP or progestin can be considered, as well as endometrial biopsy if not already performed. If medical treatment fails, surgical treatments include endometrial ablation, uterine artery embolization, hysteroscopic resection, or hysterectomy. More detail is provided below regarding adjunct evaluation and treatment in PCOS.

Heavy Menstrual Bleeding The initial evaluation for heavy menstrual bleeding includes a history and physical exam. The most common findings are a history revealing heavy menstrual bleeding coincident with menarche, indicating a disorder of hemostasis, chronic anticoagulation therapy, or an exam revealing an enlarged uterus common with leiomyomas. Von Willebrand disease (VWD) is the most common bleeding disorder associated with heavy bleeding; more than 75 % of women with VWD experience heavy menstrual bleeding [5]. Young patients may present with heavy vaginal bleeding as a first sign of coagulation disorder. The degree of suspicion about disorders of hemostasis is mostly based on history; questions sensitive in screening for this are listed in Table 1.

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Laboratory evaluation starts with ruling out pregnancy. A TSH and complete blood count should be done. Evaluation for disorders of hemostasis can be done with INR and PTT, followed by tests of platelet function and evaluation for specific coagulation factors. A transvaginal ultrasound or saline infused sonohysterogram can be done if an anatomic cause is suspected by history or examination. Ultrasound may confirm or reveal fibroids as a cause of heavy and sometimes irregular vaginal bleeding, and an endometrial lining thickness of less than 5 mm helps to reassure that heavy menstrual bleeding is not due to endometrial hyperplasia or cancer. Cultures of the cervix are helpful in those women whose history or physical examination suggests infection as an etiology. MRI is useful in identifying adenomyosis and other structural abnormalities such as leiomyomas.

A systematic review found that levonorgestrel intrauterine system, oral contraceptive pills, extended-cycle oral progestins, tranexamic acid, and NSAIDs were all effective treatments for the reduction of menstrual blood loss in women with AUB thought to be due to endometrial dysfunction. Among these, they found that levonorgestrel intrauterine system, oral contraceptive pills, and antifibrinolytics were all superior to luteal-phase progestins and recommended levonorgestrel intrauterine system over other options [8]. If the response is not adequate, imaging should be obtained if not already done.

Polyps and submucous leiomyomas can be treated by resection, uterine artery embolization, endometrial ablation, or hysterectomy. Endometrial hyperplasia should be sampled and treated. Leiomyomas can be treated with OCPs, levonorgestrel intrauterine system, or surgical resection. Possible adenomyosis can be treated with OCPs, progestin therapy, or the levonorgestrel IUD. Second-line options for leiomyomas and adenomyosis include uterine artery embolization, endometrial ablation, myomectomy, and hysterectomy.

Finally, hysterectomy is an option if the treatments above do not provide adequate relief of symptoms and childbearing is complete. Iron supplementation should be provided if anemia is present.

Bleeding Associated With Contraceptive Methods Abnormal uterine bleeding associated with hormonal contraceptive use is common. History and physical exam should be done to assess for other contributors. The possibility of infection, either cervicitis or endometritis, should be considered and cultures done as indicated.

Irregular bleeding during the first three cycles of OCP and with the use of progestin-only pills, injections, intrauterine systems, or implants is considered normal. Patients should be reassured and encouraged to continue the medication. Taking OCPs regularly can minimize irregular bleeding. Generally, higher-dose combination OCPs cause less bleeding than lower-dose formulations; if bleeding persists, the dose of the estrogen and/or progestin can be increased. Patients using progestin-only contraceptives can be treated with a 7-day course of estrogen by mouth or patch or with a cycle of combined OCP if no contraindications exist. Injections of depot medroxyprogesterone can be given 2 weeks earlier to help with irregular bleeding.

Polycystic Ovary Syndrome

Polycystic ovary syndrome is the most common endocrine abnormality in women of childbearing age. It often presents with menstrual disorders. The cause is unclear but seems to involve both genetic and environmental factors. In PCOS, insulin acts synergistically with LH to enhance androgen production by the thecal cells. It also inhibits hepatic synthesis of sex hormone binding globuin (SHBG), increasing levels of free testosterone [9]. Groups have developed different criteria for the elements of the syndrome. The National Institutes of Health (NIH) convened an evidence-based workshop in 2012 to address some

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of the discrepancies in diagnosis of the syndrome [10]. They upheld use of the inclusive Rotterdam criteria, which require at least two of these three elements and no other reason for the symptoms:

- Oligo or anovulation defined as 8 or fewer menstrual cycles per year
- Clinical (hirsutism) and/or biochemical (elevated serum testosterone levels) evidence of androgen excess
- Polycystic-appearing ovaries with 12 or more antral follicles ranging in size from 2 mm to 9 mm and increased ovarian volume of at least 10 mL

The NIH workgroup found utility in identification of four specific phenotypes for the purposes of both diagnosis and targeting treatment:

- Androgen Excess + Ovulatory Dysfunction
- Androgen Excess + Polycystic Ovarian Morphology
- Ovulatory Dysfunction + Polycystic Ovarian Morphology
- Androgen Excess + Ovulatory Dysfunction + Polycystic Ovarian

Clinical presentation may be due to any of the symptoms, including oligomenorrhea, amenorrhea, infertility, hirsutism, metabolic disturbance often manifest as diabetes, or insulin resistance of the metabolic syndrome with obesity.

A common feature in patients with PCOS is anovulation, with disruption in the usual hypothalamic, pituitary, and ovarian interactions. The resulting menstrual disorders range from amenorrhea to abnormal heavy uterine bleeding. Women with PCOS have abnormal LH levels and patterns of pulsatile release, which result in overproduction of androgens by the thecal cells of the ovary. The obesity often associated with the syndrome decreases the levels of SHBG, increasing the circulating levels of testosterone and estrogen. Usual feedback mechanisms are disrupted by chronic stimulation of hormones, and the delicate balance needed to produce ovulation is upset. Ovulation may occur from time to time in women with PCOS, and contraception should be discussed.

In addition to the virilization associated with chronic anovulation and high levels of circulating androgens and estrogens, potential consequences of PCOS include infertility, an increased risk of endometrial cancer, and possibly breast cancer. Androgen excess increases abdominal fat deposition. This fat deposition aggravates insulin resistance and produces compensatory hyperinsulinism, further enhancing ovarian androgen secretion [11]. The insulin resistance, hyperinsulinemia, and hyperandrogenism associated with the syndrome increase the risk of diabetes and heart disease.

PCOS is a diagnosis of exclusion; other causes of amenorrhea, oligomenorrhea, or abnormal bleeding patters should be sought. A targeted history and exam should be done. Most often, menstrual dysfunction related to PCOS begins at menarche and is associated with clinical findings of hyperandrogenism and obesity. Although a characteristic elevation in the LH/FSH ratio similar to that seen at mid-cycle is common, most patients are diagnosed on a clinical basis. Laboratory testing is most helpful in excluding other diagnoses, including pregnancy, hyperprolactinemia, thyroid disorders, nonclassic congenital adrenal hyperplasia, Cushing's syndrome, premature ovarian failure, menopause, medication effects, and a virilizing adrenal or ovarian tumor.

Treatment of PCOS is aimed at achieving pregnancy if desired; preventing cancers; treating associated hirsutism, alopecia, or acne; and prevention of diabetes and coronary artery disease. Lifestyle modification with diet and exercise are cornerstones of treatment, especially for those with obesity. Weight reduction alone may lead to resumption of ovulation, pregnancy for those who desire it, and significant reduction in metabolic and cardiac consequences of PCOS. Metformin is the most widely used insulin-

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Table 4 Differentiating primary from secondary dysmenorrhea

Historical points	Primary dysmenorrhea	Secondary dymenorrhea
Onset	Adolescence, within first few years of menarche	First one or two cycles after menarche for congenital outflow tract obstruction or after age 25
Menstrual flow	Normal	Heavy and/or irregular
Pain with intercourse	No	Yes
Infertility	No	Yes
History of Pelvic Inflammatory Disease	No	Maybe
Pelvic Exam	Normal	Abnormal: bulky uterus; nodular uterosacral ligaments; uterine, adnexal or cervical motion tenderness
Response to NSAIDs or OCPs	Good	Little or no response

sensitizing agent used to treat women with insulin resistance and PCOS. It decreases insulin levels and LH, with an increase in SHBG and lower circulating levels of androgens. As many as half of women with PCOS or anovulatory cycles resume regular menses after 6 months of treatment with metformin [12]. PCOS is the most common cause of anovulatory infertility. Ovulation induction alone or in combination with metformin can help achieve pregnancy. For those women who do not want to conceive, treatment is targeted at amelioration of symptoms of androgen excess and prevention of uninterrupted estrogen stimulation that can lead to endometrial cancer. Oral contraceptives help with both by interrupting the chronic estrogen stimulation, reducing the LH-mediated androgen production, and increasing SHBG. For those with contraindications to estrogen, endometrial protection can be achieved with cyclic oral progesterone, with a goal of a withdrawal bleed at least every 90 days. Progestin-only contraceptives including intrauterine devices, implants, and injections are an alternative for endometrial protection but are often associated with abnormal bleeding patterns [13]. Antiandrogens including spironolactone, flutamide, and finasteride are effective in treating hirsutism and alopecia but have not been shown to augment the effects of oral contraceptives [12]. Antiandrogens may need to be used for 6 months before noting improvement. Screening for diabetes and monitoring lipid profiles is recommended, especially in obese patients.

Dysmenorrhea

Dysmenorrhea is defined as cramping pain in the lower abdomen with menses. Dysmenorrhea is described as primary when there is no discernible pelvic pathology or secondary due to pelvic pathology, most often endometriosis. Primary dysmenorrhea is a diagnosis of exclusion. A thorough history and physical examination will help determine if there is pelvic pathology. Table 4 lists elements helpful in differentiating primary from secondary dysmenorrhea.

Primary Dysmenorrhea

Primary dysmenorrhea is the most common menstrual disorder. Pain usually presents in sharp and intermittent spasms, centered in the suprapubic area. Pain may radiate to the back of the legs or the low back. Systemic symptoms of nausea, vomiting, diarrhea, fatigue, fever, headache, or light-headedness are fairly common. Pain usually begins within hours of the onset of menses and peaks within the first 1–2 days. Most symptoms can be explained by the action of uterine prostaglandins, particularly PGF2. This prostaglandin is released as the endometrium sloughs, causing uterine contractions.

Secondary Dysmenorrhea

The onset of secondary dysmenorrhea is generally later in life than primary, often the mid-twenties. The pelvic pathology may be uterine or extrauterine. Uterine causes of secondary dysmenorrhea are

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adenomyosis, pelvic inflammatory disease, cervical stenosis, polyps, fibroids, and intrauterine devices. Extrauterine causes are endometriosis; inflammation and scarring due to adhesions; functional ovarian cysts; benign or malignant tumors of the ovary, bowel, or bladder; and inflammatory bowel disease. Some of these disorders can be diagnosed with a careful pelvic exam. Imaging with transvaginal ultrasound, MRI, or direct visualization with laparoscopy is often needed to make a certain diagnosis in secondary dysmenorrhea. Additional testing may be needed to evaluate for pelvic inflammatory disease or inflammatory bowel disorders.

Treatment of Dysmenorrhea A Cochrane review of 73 randomized controlled trials demonstrated strong evidence in support of the use of nonsteroidal anti-inflammatory drugs (NSAIDs) as first-line treatment of primary dysmenorrhea [14]. No specific NSAID has been proven more effective than others, and all are most effective when begun 1–2 days prior to anticipated menses and continued for several days. For those unresponsive to NSAIDs or who desire contraception, hormonal contraceptives including estrogen and progesterone combinations as well as progestin-only preparations are the next treatment options. These are delivered orally, intravaginally, topically, via intrauterine systems, or via subcutaneous or intramuscular depots.

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Menopause

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Overview

Menopause is a natural occurrence that marks the end of woman's reproductive years. In layman's terms, 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 menopausal symptoms.

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 [3–5]. 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 [4]. 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) [6, 7]. 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 [8, 9].

The hallmark of the menopausal transition (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 in their health.

Specifically, women may desire to know "what to expect" with regard to the timeline of menopause and their menstrual cycles. Such questions can be challenging for the family physician to address, since the menopausal transition is seemingly 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 menopausal transition.

The Stages of Reproductive Aging Workshop (STRAW) originally met in 2001 [10] to discuss the existing data on the menopausal transition. 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 menopausal transition. The

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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

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 [9]. 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 menopausal transition, 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. Studies [12, 13] suggest that inhibin B secreted by the developing follicles plays an important role, leading to high but variable levels of FSH resulting in changes of bleeding patterns.

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 [9] 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 10 cycles [9].

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, episodes of amenorrhea, and an

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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 menopausal transition. 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 final menstrual period (FMP). This stage has additional clinical significance, as 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.

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 [14].

Epidemiology

The average onset of menopause is 51 years of age. 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 [7, 15]. This variation is thought to be due to a number of factors. Women with family members with early menopause are more likely to also experience early menopause [16]. Menopause occurs earlier in women of Hispanic or Japanese decent when compared to Caucasian women [17]. Lastly, smoking causes menopause to occur earlier [18–20].

Systemic Effects of Menopause

Menopause reflects a time of significant change for women. All of the effects discussed below can have a substantial biopsychosocial impact, and they represent opportunities for the family physician to improve the quality of life in women. The sequelae of menopause are widely underreported, and intentional screening should be considered part of high-quality care for perimenopausal and postmenopausal women.

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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" [21]. 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 [22]. Peri- and postmenopausal women are apparently predisposed to these reactions due to a narrowing of the thermoregulatory set zone in the hypothalamus [23]. 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 [9, 24]. Data on the duration of VMS suggest that the average length of symptoms is 4–5 years, but a subset of women will continue to have troublesome symptoms for 10 years or more [25, 26]. 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. 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 [14, 21]. 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 replacement therapy. Other nonhormonal treatments that may reduce symptoms include paroxetine, venlafaxine, clonidine, and gabapentin [21]. Currently, no over-the-counter agents have been shown to have clear benefit in reducing VMS [14, 27].

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 % percent of peri- and postmenopausal women reported sleep difficulty [28]. The menopausal transition has been shown in multiple studies to be strongly associated with sharp increases in the incidence of sleep disturbance and insomnia. However, there are numerous potential causes for sleep disruption in peri- and postmenopausal women, and in any given patient, a number of 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 [28]. Primary sleep disorders such as obstructive sleep apnea, restless leg syndrome, and periodic limb movement disorder all present with increased frequency in menopausal women [29]. 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 a large number of worsening general medical conditions can contribute to poor sleep. Medications should be reviewed, and sources of chronic and acute pain should be actively managed. Lastly, the available evidence suggests that the hormonal changes of menopause alone contribute to decreased quality of sleep [29].

In summary, the approach to sleep disturbance in perimenopause must be highly individualized and involve careful attention to the patient's specific complaints. As in all age groups, standard sleep hygiene education should be provided. The patient's unique risk factors for sleep disturbance should be addressed. Lastly, hormonal replacement therapy may be considered for sleep disturbances, particularly in women

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who have other menopausal symptoms. The majority of studies that have assessed the effect of HRT on sleep have reported some degree of improved sleep over placebo [29].

Urogenital Changes

Essentially all of the tissues of the lower genitourinary tract in females feature estrogen receptors, including the bladder, urethra, and pelvic floor musculature [22]. With the withdrawal of estrogen during menopause, these structures undergo a number of 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 [30]. Some women will begin to experience symptoms in the perimenopausal time frame, but prevalence increases steadily in the postmenopausal period [31]. The most commonly reported GSM symptoms are vaginal dryness and dyspareunia. 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. Urinary tract changes, such as urinary frequency, dysuria, and increased susceptibility to UTIs are thought to be at least partially attributable to the hormonal changes of menopause [32].

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 [21, 32].

Once the diagnosis of GSM is established, women should be reassured of the possibility of treatment. Family physicians should bear in mind that the symptoms of vulvovaginal atrophy are unlikely to improve without intervention [21]. 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 [30]. Patients should be appropriately counseled on the unstudied safety profile of long-term use [21]. In women with additional menopausal symptoms, oral hormone replacement therapy (HRT) can be considered, as it is also effective for the symptoms of GSM.

Cognitive Changes

Many women perceive changes in their cognition during the menopausal transition. Memory loss or forgetfulness is one of the most common complaints, but women may also report a decreased ability to concentrate or multitask [14]. Studies investigating this phenomenon have validated some degree of correlation between subjective complaints and objective cognitive performance [33]. 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 [14]. However, in a given patient, confounding factors may be in play. Subjective cognitive complaints are more common in the presence of mood symptoms and vasomotor symptoms.

Although a number of trials suggest modest cognitive benefit from HRT, conflicting evidence exists [34]. The North American Menopause Society does not recommend HRT 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 [14].

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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 [35]. Interestingly, this risk is most prominent in women with a history of past depression, premenstrual disorder, or postpartum depression [36], suggesting vulnerability to affective disorders in times of hormonal fluctuation. Women with vasomotor symptoms are also at significant risk.

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 [14].

Skin and Hair Changes

The hormonal changes of menopause represent one of the several factors driving the process of skin aging in postmenopausal women. General systemic aging, along with variables such as sunlight exposure and smoking, plays significant roles as well. In general, postmenopausal women may notice thinning of the skin, increased skin laxity and wrinkles, and dryness of the skin [14, 37].

With regard to the hair, women may note hair loss or occasionally hirsutism. Both of these changes may potentially 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 [14].

Interestingly, estrogen replacement therapy has been shown to improve various characteristics of both the skin and hair in postmenopausal women [14, 37]; 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. It is well known that premenopausal women have, on average, more favorable lipid profiles than men [22]. However, this advantage subsides at menopause, and cardiovascular disease (CVD) remains the number one cause of death in women [14, 22]. Specifically, LDL levels increase and HDL levels decrease as a result of the menopausal transition [22]. The effect of hormonal changes on female lipid profiles led to a large-scale investigation of HRT for reduction of CV risk, with the ultimate finding of inadequate benefit and unacceptable risk for routine use of HRT in CVD prevention.

Family physicians should be aware of the potential for abrupt changes in lipid profiles in the early postmenopausal period [14]. 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

The estrogen deficiency of menopause promotes osteoclast activation, leading to a state in which bone reabsorption exceeds bone formation [38]. 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 [39].

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

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average-risk women at age 65. Earlier DEXA screening, however, should be considered in postmenopausal women thought to be at increased risk for osteoporosis [14]. 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 [39]. 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 [39]. However, family physicians should be aware that a definitive fracture reduction benefit from supplementation has not yet been proven [40].

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 [39]. 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 [39]. 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 [41]. Hormone therapy (HT) has been the mainstay treatment of menopausal symptoms for over 60 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 nonhormonal therapies.

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. Progesterone alone also reduces vasomotor symptoms but not as effectively as estrogen [42].

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. Up until the 1990s, HT was thought to be potentially beneficial, not only for treatment of menopausal symptoms but also for prevention of chronic diseases. Until the publication of the Women's Health Initiative (WHI) in 2002 [43, 44], HT was widely prescribed for the prevention of cardiovascular disease, dementia, and osteoporosis. The Women's Health Initiative, in contrast to

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previously believed benefit, showed significant risks associated with HT use and even possible worsening of coronary vascular disease (CVD) that it was being prescribed to prevent. In fact, risk for fracture was the only outcome with strong evidence of benefit from HT. This benefit occurred only after 4–5 years of therapy. Although it is not approved by the FDA for the treatment of osteoporosis, it is generally recommended that HT for the prevention of fracture be reserved for high-risk women in whom other therapies are contraindicated [45]. Overall, the physician's decision to offer treatment of vasomotor symptoms may depend on a woman's perception of the severity of symptoms [41].

Effectiveness of Hormone Therapy

Hormone therapy has been consistently shown to be effective at decreasing vasomotor symptoms. Meta-analysis of randomized controlled trials shows incidence of hot flashes with HT reduced by 75 % compared to 50 % reduction with placebo [41]. Stated another way, estrogen has been shown to reduce the frequency of hot flashes by approximately 2.5–3 hot flashes per day [44]. In addition to decreased risk of fractures, HT may offer a small to moderate improvement in sexual function [45]. Improvement in sexual function seems to occur via treatment of menopausal symptoms. Treating other aspects of sexual function with HT is not supported by evidence [46]. Improvements in vasomotor symptoms and vaginal dryness can take, on average, 1–2 months after starting therapy [41].

Formulations

Hormone therapy is available in oral tablets, transdermal patches, and topical or intravaginal preparations. Most women start at a low dose of oral conjugated equine estrogen (Premarin) 0.3 mg or 0.5–1.0 mg of oral or transdermal 17-beta-estradiol (Estrace, Climara, Alora) or intravaginal estradiol valerate (Delestrogen). Dosage can be increased to 1.25 mg daily of conjugated equine estrogens if symptoms are not relieved. Estrogen alone can be used in women without a uterus. However, unopposed estrogen in women with a uterus increases the risk of endometrial hyperplasia [47]. Progesterone, however should be added to estrogen in any woman with a uterus [45]. There is minimal systemic absorption of topical agents, so topical estrogen formulations are safe to use in women with a uterus without the addition of progesterone. Progesterone formulations with a minimum of 1 mg norethindrone (Ortho Micronor, Nor-QD) or 1.5 mg medroxyprogesterone acetate have been shown to be safe as the risk of endometrial hyperplasia has not been found to be significantly different than with placebo. Pre-packaged products simplify the use but may not be available in low doses. Low doses of progesterone can be obtained from progesterone-only pills such as Norethisterone. Continuous regimens of combined estrogen plus progesterone (Prempro) daily can be used in women with a uterus who have been postmenopausal for more than 1 year. Within 1 year of the last menstruation, regimens of daily estrogen with progesterone 10–14 days per month are indicated. For those women who are still menstruating, estrogen should be started on the first day of the menstrual bleeding with progesterone given 14 days later, resulting in withdrawal bleeding around the same time menstruation would be expected [41].

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 [41, 42].

The Women's Health Initiative [41, 43, 48] unveiled many previously unknown risks associated with HT. Studies demonstrated that both ET and EPT therapies increased risk for stroke, coronary vascular disease (CVD), venous thromboembolism (VTE), pulmonary embolus (PE), dementia, and gallbladder disease. Treatment with combined hormone therapy, but not with estrogen alone, increased the risk of breast cancer [45].

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Table 2 Risk of combined hormone therapy in postmenopausal women

Complication	Years of use	Absolute risk (AR)
Coronary event	After 1 year	4 per 1,000
Venous thromboembolism	After 1 year	7 per 1,000
Stroke	After 3 years	18 per 1,000
Breast cancer	After 5.6 years	23 per 1,000
Gallbladder disease	After 7 years	27 per 1,000
Death from lung cancer	After 5.6 years (plus 2.4 years of follow-up)	9 per 1,000
Dementia (>65 years, healthy)	After 4 years	18 per 1,000

Adapted from Marjoribanks et al. [45]

Table 3 Risk of estrogen-only hormone therapy in peri- and postmenopausal women

Complication	Years of use	Absolute risk (AR)
Coronary event	After 1 year	4 per 1,000
Venous thromboembolism	After 1–2 years After 7 years	5 per 1,000 21 per 1,000
Stroke	After 7 years	32 per 1,000
Gallbladder disease	After 7 years	45 per 1,000
Breast cancer	No significant increased risk	

Adapted from Marjoribanks et al. [45]

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 2 and 3).

When using this data to counsel women on the risks and benefits of HT, there are caveats and nuances to keep in mind. The majority of 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). Among women with CV disease, long-term use of EPT increased the risk for VTE. Women taking long-term HT, either ET or EPT, had decreased incidence of fractures [45]. Subgroup analysis suggests that CVD was slightly reduced, rather than increased, in women who were closer to menopause at time of initiation. Additionally, combination HT initiated closer to menopause resulted in somewhat increased risk of breast cancer [49]. Overall, there are limitations with the currently published data, as studies to date have not been designed to specifically evaluate the effect of HT in perimenopausal or younger-aged women. 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.

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

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ongoing need for continued therapy versus a trial off of therapy. 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, although topical therapy may be sufficient [41]. 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 seems appropriate.

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 that include antidepressants, clonidine, gabapentin, plant derivatives, 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). There has also been concern that the efficacy of antidepressants may be decreased in women with a history of breast cancer taking tamoxifen (Soltamox) [44]. This may be due to metabolism of both tamoxifen and some antidepressants through the cytochrome P-450 pathway [41]. Women with history of breast cancer taking tamoxifen are among the most likely to need nonhormonal therapy.

Paroxetine (Paxil): Studies [44] 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 per 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 per 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. Women who used tamoxifen had similar results [44]. Most recently, a 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 eight per day, venlafaxine resulted in reduction to 5.5 daily episodes compared to 4.4 in the estradiol group [50]. Additional studies [44] have been done with other antidepressants including fluoxetine (Prozac) and citalopram (Celexa) 30 mg daily with neither showing significant difference.

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 [44]. Transdermal clonidine at 0.1 mg appears more effective than oral clonidine [41].

Gabapentin (Neurontin): At doses of 900 mg per day, gabapentin has been shown to be effective at reducing hot flashes in women with breast cancer, including those taking tamoxifen. Smaller doses of 300 mg per day were not shown to be effective [44].

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 show some potential, although with slight

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Table 4 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)
Sleep[a]	Insomnia Poor quality of sleep		Sleep hygiene Cognitive behavioral therapy (CBT) Exercise
Urogenital	Vaginal dryness, irritation, pain Dyspareunia Urinary frequency Dysuria Increased susceptibility to UTIs	ET (Transdermal, intravaginal)	
Psychological	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

benefit. Meta-analysis of red clover isoflavones, specifically Promensil and Rimostil, also showed possible slight benefit [44, 51]. Black cohosh, an herbal remedy, has shown mixed results, with possible benefit over placebo in women who have breast cancer. Vitamin E has minimal benefit over placebo, resulting in one less hot flash daily. A number of other natural products including evening primrose oil, dong quai, and ginseng have shown no benefit [41].

Exercise: Current literature is mixed regarding the relationship between physical activity and hot flashes. Physical activity, as an acute trigger of hot flashes, has been anecdotally reported, but there has

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been little investigation. There are ongoing studies about the role of leisure activities versus non-leisure activities and sleep in menopausal women with vasomotor symptoms. Women with higher rates of non-leisure activity actually reported increased sleep [52]. 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 menopausal symptoms.

Acupuncture: Acupuncture has also been tried for combating menopause symptoms. According to a 2013 Cochrane Review, a meta-analysis of eight studies that included 1,115 women concluded there is insufficient evidence to support its use in vasomotor symptoms [53] Table 4.

Not all women will experience menopausal-related symptoms needing 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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Family Medicine
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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. However, since many leiomyomata are asymptomatic, the true incidence is unknown. African-American women have a threefold higher incidence than white, Hispanic, or Asian women [2]. In addition, obese and nulliparous women and those with early menarche or infertility have a higher incidence [3].

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 (6) 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.

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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 leiomyomata (6 cm in 1 year), less than 0.1 % of these are malignant. At surgery for women with a leiomyoma, less than 0.25 % have sarcoma. 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.

Referrals

For women whose symptoms continue despite treatment with medications, there are several 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. For women wishing to preserve their fertility and not wanting surgery, uterine artery embolization can be used. 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. Finally, hysterectomy may be offered as a definitive procedure. An 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].

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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		

Counseling
Fibroid tumors can be present in women with recurrent implantation failure, and appropriate counseling regarding their treatment would fall on the family physician [4]. 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 % [5]. Three WNT/beta-catenin pathway inhibitors, inhibitor of beta-catenin and TCF4 (ICAT), niclosamide, and XAV939, have been shown to block leiomyoma growth and proliferation [6]. Finally, a number of substances have been effective in the chemoprevention of fibroid tumors in quails [7, 8].

Endometrial Carcinoma

General Principles

Definition/Background
Endometrial cancer is the most common gynecologic malignancy and the fourth most common cancer in women after breast, lung, and colorectal cancers [9]. In the last 8 years, both the incidence and death rate from endometrial cancer have increased [9]. Various theories to explain this increase included increasing life span and coexisting medical comorbidities in these women.

Epidemiology
The mean age at diagnosis is 61 years, and 90 % of cases occur in women older than 50 years. Twenty percent of women have this diagnosis before menopause, and approximately 5 % have disease before age 40 [10]. Approximately 72 % are stage I, 12 % are stage II, 13 % are stage III, and 3 % are stage IV.

Classification
Endometrial cancer is commonly classified into three types (Table 1: Classification of Endometrial Cancer). 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.

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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 and 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 [11]. 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 [12]. 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 [13]. 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 [14]. 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 [15]. 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 [16].

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 [17]. There have been a few retrospective studies comparing its accuracy to dilation and curettage (D&C) [18]. Although D&C was slightly better, D&C 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 [19]" recommend beginning the evaluation with endovaginal ultrasound (EV-US). If the endometrial stripe is </4 mm in postmenopausal

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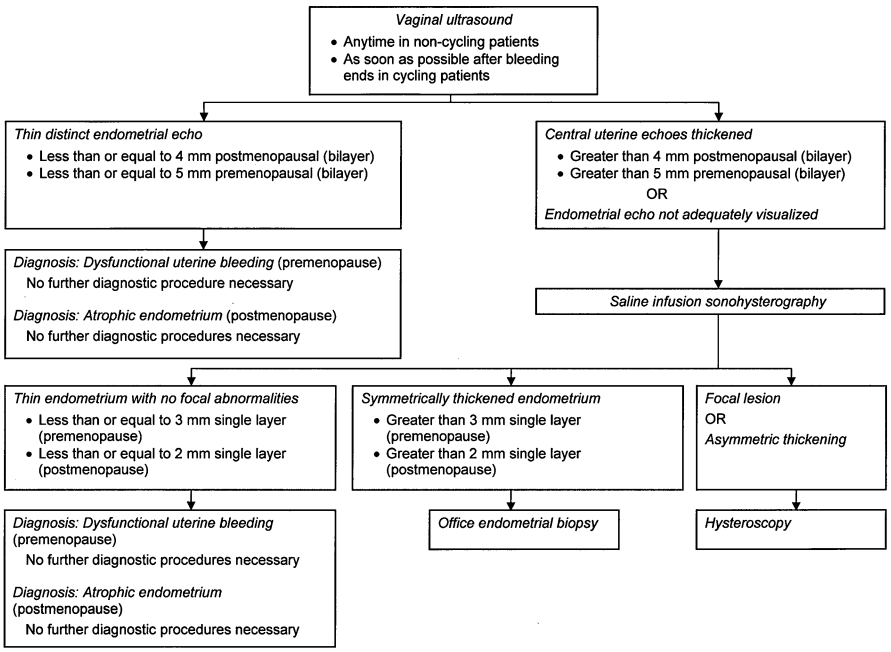

Fig. 1 Ultrasonography-based triage for patients with abnormal uterine bleeding (Originally published in Obstetrics & Gynecology 2010 [20], published with kind permission of Wolters Kluwer Health. All rights reserved)

women or </5 mm in premenopausal women, no further diagnostic procedure is necessary (Fig. 1-Goldstein [20]). 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; or women whose bleeding did not respond to medical therapy [21]. All women >/35 years with suspected anovulatory bleeding should have an EMB performed.

Special Testing

As noted above, Goldstein includes saline infusion sonohysterography in the workup. The benefit of adding hysteroscopy to sonography and biopsy is unclear. A retrospective chart review of more than 400 hysteroscopy/D&C procedures demonstrated that hysteroscopy correctly identified 52 % of patients with hyperplasia and 20 % of those with carcinoma. A negative hysteroscopic impression was not sufficient to exclude the diagnosis of hyperplasia or carcinoma [22].

Differential Diagnosis

The differential diagnosis for abnormal uterine bleeding includes both malignancy as discussed above and benign causes. An ACOG Practice Bulletin [23] reviews benign causes, as does Chapter "► Diseases of the Prostate" in this text. 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 [24]. 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 [13]. Cyclic medroxyprogesterone 10 mg daily for 14 days each month and 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

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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 [25]. 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 10 mg daily for 14 days each month and 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 [9]. 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 [26]. Epidemiology, risk factors, diagnosis, screening, prevention, and treatment will be reviewed here.

Epidemiology

Worldwide, cervical cancer is the second most common malignancy [27]. It is estimated that there will be 12,360 new cases of cervical cancer and 4,020 cervical cancer-related deaths in the United States in 2014. Cervical cancer estimates are higher for particular racial and ethnic groups with incidence and mortality being higher in non-white than white women in the United States [28]. The incidence is highest in Hispanics/Latinos at 12.5 per 100,000 and mortality highest in African-Americans with 4.4 deaths per 100,000 cases. There has been an overall decrease of deaths by 30.66 % from 1990 to 2007 [29] and a 50 % reduction in incidence over 30 years from 1975 to 2006 [30].

Risk Factors

Epidemiological risk factors for cervical cancer are well documented. Some are modifiable and speak 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 including early onset of sexual activity, multiple sexual partners, history

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Table 2 Risk factors for cervical cancer [34]

Risk factor	Relative risk
Menarche to first coitus < 1 year	26.4
Age at first coitus < 16 years	16.1
More than 3 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

of sexually transmitted infections, sexual partner (s) infected with HPV, history of vulvar or vaginal intraepithelial neoplasia or cancer, and immunosuppression [31]. In utero diethylstilbestrol (DES), previous treatment of high-grade precancerous lesions, and history of cervical cancer are also risk factors [32]. Socioeconomic status, three or more full term births, young age at first delivery (<20 years of age), and oral contraceptive use may also increase risk. Smoking is associated with an increased risk of squamous cell carcinoma. 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 [33] (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 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, and (4) follow the patient for evidence of recurrence and/or treatment-related complications [27].

History

Early cervical cancer may be asymptomatic. Common symptoms of cervical cancer include irregular vaginal bleeding, heavy vaginal bleeding, and postcoital bleeding [31]. Vaginal discharge may also be described and can be purulent, malodorous, bloody, watery, or mucinous [35]. Taking a careful history and proper diagnostic testing must be performed as to not mistaken 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 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 [31].

Physical Examination

When a woman presents with a history and 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 and 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.

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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 is typically not used for the diagnosis of cervical cancer, but is useful in staging and evaluation of women with a known malignancy.

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

This 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 [27] and should be performed by an experienced clinician. Staging does not include lymph node involvement, though lymph node evaluation must be performed as information regarding involvement affects treatment planning. The most common metastatic sites include the aortic and mediastinal lymph nodes, lungs, and skeleton.

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.

Referrals

Patients diagnosed with 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 are helpful for the patient as they are coping with a new diagnosis or recurrent cervical cancer.

Screening

In 2012 the US Preventive Services Task Force (USPSTF) updated the 2003 statement on screening for cervical cancer. These recommendations are similar to the ACS/ASCCP/ASCP and ACOG current guidelines.

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 [32]. Sexual history is not taken into account in the recommendations. Screening recommendations from the USPSTF including techniques, initiation, frequency, and management of abnormal screening results will be discussed here.

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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 ACOG [33]. 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 based on guidelines set forth by US Preventive Services Task Force in 2012, ACS/ASCCP/ASCP, and ACOG [32, 33] (Fig. 2). 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.

The ASC identifies groups that may require more frequent testing including individuals with HIV, immunosuppression, and in utero exposure to DES. For HIV patients, ACOG recommends a screening Pap smear twice in the first year after diagnosis and then annually thereafter [36].

All guidelines mentioned above for cervical cancer screening recommend cytology alone for screening every 3 years for women aged 21–29 years. 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 [37]. For women between the ages of 30 and 65 years, cytology alone can be performed every 3 years according to the USPSTF guidelines [32]. The USPSTF states that in this age group, women who wish to extend screening to every 5 years may do 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.

The USPSTF recommends stopping cervical cancer screening for women older than age 65 with adequate prior screening, not otherwise at risk for cervical cancer [32]. This recommendation defines adequate screening as two consecutive cytology-negative Pap smears with negative HPV co-testing in the 10 years prior to stopping with the last test within 5 years or three consecutive negative cytology 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 [32]. Women who have had a high-grade precancerous lesion should continue testing for 20 years after management of the lesion.

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 two revisions since 1988. 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 screening tests, CIN, and adenocarcinoma in situ (AIS) [38]. 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).

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

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Cervical Cancer Screening Guidelines for Average-Risk Women [1]

	American Cancer Society (ACS), American Society for Colposcopy and Cervical Pathology (ASCCP), and American Society for Clinical Pathology (ASCP) [2] 2012	U.S. Preventive Services Task Force (USPSTF) [3] 2012	American College of Obstetricians and Gynecologists (ACOG) [4] 2012
When to start screening [5]	Age 21. Women aged <21 years should not be screened regardless of the age of sexual initiation or other risk factors. *(Strong recommendation)*	Age 21. *(A recommendation)* Recommend against screening women aged <21 years. *(D recommendation)*	Age 21 regardless of the age of onset of sexual activity. Women aged <21 years should not be screened regardless of age at sexual initiation and other behavior-related risk factors. *(Level A evidence)*
Statement about annual screening	Women of any age should not be screened annually by any screening method. *(Strong recommendation)*	Individuals and clinicians can use the annual Pap test screening visit as an opportunity to discuss other health problems and preventive measures. Individuals, clinicians, and health systems should seek effective ways to facilitate the receipt of recommended preventive services at intervals that are beneficial to the patient. Efforts also should be made to ensure that individuals are able to seek care for additional health concerns as they present.	In women aged 30–65 years, annual cervical cancer screening should not be performed. *(Level A evidence)* Patients should be counseled that annual well-woman visits are recommended even if cervical cancer screening is not performed at each visit.
Screening method and intervals [6]			
Cytology (conventional or liquid based) 21-29 years of age	Every 3 years. [7] *(Strong recommendation)*	Every 3 years. *(A recommendation)*	Every 3 years. *(Level A evidence)*
Cytology (conventional or liquid based) 30-65 years of age	Every 3 years. [7] *(Strong recommendation)*	Every 3 years. *(A recommendation)*	Every 3 years. *(Level A evidence)*
HPV co-test (cytology + HPV test administered together) 21-29 years of age	HPV co-testing should not be used for women aged <30 years.	Recommend against HPV co-testing women aged <30 years. (D recommendation)	HPV co-testing [8] should not be performed in women aged < 30 years. *(Level A evidence)*
HPV co-test (cytology + HPV test administered together) 30-65 years of age	Every 5 years *(Strong recommendation)*; this is the preferred method *(Weak recommendation)*.	For women who want to extend their screening interval, HPV co-testing every 5 years is an option. (A recommendation)	Every 5 years; this is the preferred method. *(Level A evidence)*
Primary HPV testing [9]	For women aged 30-65 years, screening by HPV testing alone is not recommended in most clinical settings. *(Weak recommendation)* [10]	Recommend against screening for cervical cancer with HPV testing (alone or in combination with cytology) in women aged <30 years. *(D recommendation)*	Not addressed.
When to stop screening	Aged >65 years with adequate screening history. [11,12]	Aged >65 years with adequate screening history. *(D recommendation)* [11]	Aged >65 years with adequate screening history [11, 13] *(Level A evidence)*
Screening post-hysterectomy	Women who have had a total hysterectomy (removal of the uterus and cervix) should stop screening. [14] Women who have had a supra-cervical hysterectomy (cervix intact) should continue screening according to guidelines. *(Strong recommendation)*	Recommend against screening in women who have had a hysterectomy (removal of the cervix). [13] *(D recommendation)*	Women who have had a hysterectomy (removal of the cervix) should stop screening and not restart for any reason. [13] *(Level A evidence)* [15]

Fig. 2 (continued)

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The need for a bimanual pelvic exam	Not addressed in 2012 guidelines but was addressed in 2002 ACS guidelines. [16]	Addressed in USPSTF ovarian cancer screening recommendations (draft). [17]	Addressed in 2012 well-woman visit recommendations.[18] **Aged <21 years**, no evidence supports the routine internal examination of the healthy, asymptomatic patient. An "external-only" genital examination is acceptable. **Aged ≥21 years**, no evidence supports or refutes the annual pelvic examination or speculum and bimanual examination. The decision whether or not to perform a complete pelvic examination should be a shared decision after a discussion between the patient and her health care provider. Annual examination of the external genitalia should continue.[19]
Screening among those immunized against HPV 16/18	Women at any age with a history of HPV vaccination should be screened according to the age specific recommendations for the general population.	The possibility that vaccination might reduce the need for screening with cytology alone or in combination with HPV testing is not established. Given these uncertainties, women who have been vaccinated should continue to be screened.	Women who have received the HPV vaccine should be screened according to the same guidelines as women who have not been vaccinated. *(Level C evidence)*

HPV = human papillomavirus; CIN = cervical intraepithelial neoplasia

[1] These recommendations do not apply to women who have received a diagnosis of a high-grade precancerous cervical lesion (CIN 2 or 3) or cervical cancer, women with in utero exposure to diethylstilbestrol, or women who are immunocompromised, or are HIV positive.

[2] Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. CA Cancer J Clin. 2012 May-Jun;62(3):147-72. doi: 10.3322/caac.21139. Available at http://www.cancer.org/Cancer/CervicalCancer/DetailedGuide/cervical-cancer-prevention

[3] USPSTF. Screening for Cervical Cancer. 2012. Available at http://www.uspreventiveservicestaskforce.org/uspstf11/cervcancer/cervcancerrs.htm. These recommendations apply to women who have a cervix, regardless of sexual history.

[4] ACOG Practice Bulletin No. 131: Screening for Cervical Cancer. ACOG Committee on Practice Bulletins-Gynecology. *Obstet Gynecol.* 2012 Nov;120(5):1222-38. doi: http://10.1097/AOG.0b013e318277c92a

[5] Since cervical cancer is believed to be caused by sexually transmissible human papillomavirus infections, women who have not had sexual exposures (e.g., virgins) are likely at low risk. Women aged >21 years who have not engaged in sexual intercourse may not need a Pap test depending on circumstances. The decision should be made at the discretion of the women and her physician. Women who have had sex with women are still at risk of cervical cancer. 10-15% of women aged 21-24 years in the United States report no vaginal intercourse (Saraiya M, Martinez G, Glaser K, et al *Obstet Gynecol.* 2009 Dec;114(6):1213-9. doi: 10.1097/AOG.0b013e3181be3db4.). Providers should also be aware of instances of non-consensual sex among their patients.

[6] Conventional cytology and liquid-based cytology are equivalent regarding screening guidelines, and no distinction should be made by test when recommending next screening.

[7] There is insufficient evidence to support longer intervals in women aged 30-65 years, even with a screening history of consecutive negative cytology tests.

[8] All ACOG references to HPV testing are for high risk HPV testing only. Tests for low risk HPV should not be performed.

[9] Primary HPV testing (HPV testing alone) is defined as conducting the HPV test as the first screening test. It may be followed by other tests (like a Pap) for triage.

[10] No further explanation of which clinical settings HPV testing should be used to screen women aged 30-65 years as a stand alone test.

[11] Current guidelines define adequate screening as three consecutive negative cytology results or two consecutive negative co-tests within 10 years before cessation of screening, with the most recent test performed within 5 years, and are the same for ACS, ACOG, and USPSTF.

[12] Women aged >65 years with a history of CIN2, CIN3, or AIS should continue screening for at least 20 years after spontaneous regression or appropriate management. (Weak recommendation)

[13] And no history of CIN 2 or higher.

[14] Unless the hysterectomy was done as a treatment for cervical pre-cancer or cancer.

[15] Women should continue to be screened if they have had a total hysterectomy and have a history of CIN 2 or higher in the past 20 years or cervical cancer ever. Continued screening for 20 years is recommended in women who still have a cervix and a history of CIN 2 or higher. Therefore, screening with cytology alone every 3 years for 20 years after the initial post-treatment surveillance for women with a hysterectomy is reasonable. (Level B evidence)

[16] 2002 guidelines statement: The ACS and others should educate women, particularly teens and young women, that a pelvic exam does not equate to a cytology test and that women who may not need a cytology test still need regular health care visits including gynecologic care. Women should discuss the need for pelvic exams with their providers. Saslow D, Runowicz CD, Solomon D, et al. American Cancer Society Guideline for the Early Detection of Cervical Neoplasia and Cancer. *CA Cancer J Clin* 2002; 52: 342-362.

[17] The bimanual pelvic examination is usually conducted annually in part to screen for ovarian cancer, although its effectiveness and harms are not well known and were not a focus of this review. No randomized trial has assessed the role of the bimanual pelvic examination for cancer screening. In the PLCO Trial, bimanual examination was discontinued as a screening strategy in the intervention arm because no cases of ovarian cancer were detected solely by this method and a high proportion of women underwent bimanual examination with ovarian palpation in the usual care arm.

[18] ACOG Committee Opinion No. 534: Well-Woman Visit. Committee on Gynecologic Practice. *Obstet Gynecol.* 2012 Aug;120(2)1:421-24. doi: 10.1097/AOG.0b013e3182680517.

[19] For women aged ≥21 years, annual pelvic examination is a routine part of preventive care even if they do not need cervical cytology screening, but also lacks data to support a specific time frame or frequency of such examinations. The decision to receive an internal examination can be left to the patient if she is asymptomatic and has undergone a total hysterectomy and bilateral salpingo–oophorectomy for benign indications, and is of average-risk.

Fig. 2 Cervical cancer screening guidelines (http://www.cdc.gov/cancer/cervical/pdf/guidelines.pdf)

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2012 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, 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, and 35 are associated with moderate (CIN 2) and severe dysplasia (CIN 3). 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 [33].

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 two 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, CIN 1, CIN 2, and adenocarcinoma in situ caused by oncogenic HPV genotypes 16 and 18 [39]. The quadrivalent three-dose vaccine is approved for females and males ages 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, and vagina and genital warts associated with the aforementioned genotypes [40].

The American Academy of Pediatrics (AAP) and CDC recommend that girls ages 11–12 years be routinely immunized with three doses of HPV4 or HPV2 and that all girls and women ages 13 through 26 years who have not completed the series should complete the series [41]. The AAP and CDC also recommend that all boys 11–12 years of age are immunized routinely with three doses of HPV4 and if they are ages 13–26 they should complete the series if they have not already [41]. Both vaccines can be given as early as the age of 9.

Long-term effects of HPV vaccination on prevention of cervical cancer and CINs 2 and 3 are unknown, and there are no current trials that provide data on long-term efficacy [42]. 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, women who have been vaccinated against high-risk HPV infection should continue to be screened according to the USPSTF guidelines [32].

Secondary Prevention

The Pap smear is a screening tool used to detect changes in cervical cells. In 2012, 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 2001 Bethesda System terminology [43] is used for cytological classification. Using the algorithms set forth in the ASCCP 2012 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

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HPV testing only refers to high-risk, oncogenic HPV types only. The 2012 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 [9]. The majority of ovarian malignancies, approximately 95 %, are derived from epithelial cells. Epithelial carcinomas 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 2014, there were 21,980 expected cases of ovarian cancer to be diagnosed, with an expected 14,270 deaths in the United States [9]. It is the fifth leading cause of death among women in the United States [9]. Based on data from 2009 to 2011, approximately 1.3 % of women will be diagnosed with ovarian cancer during their lifetime, and in 2011, the number of women living with ovarian cancer in the United States was 188,867 [44]. Rates for new ovarian cancer in the United States have been falling on average 1.1 % for the past 10 years [44]. Most ovarian cancers, 70–75 %, are found at stages III to IV, and the overall 5-year survival rate is 20–30 % [45]. The 5-year survival rate for ovarian cancer found at stage I is 90–95 % [45].

Risk Factors

The pathogenic mechanisms for ovarian cancer have yet to be explained. Currently, there are two 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.

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 germ line 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 infertility, early menarche, and late menopause may be at an increased risk.

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The Women's Health Initiative found no increased risk for women on combined estrogen-progestin therapy compared with placebo [46].

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 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 [47].

Others

Obesity seems to increase the risk of ovarian cancer [48]. Risk also increases with age.

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 [49, 50]. 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 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 are 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 two 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.

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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 [45] outlines criteria that, if met, would prompt a clinician to refer a patient for a genetic risk assessment. Women with an approximately 20–25 % chance of having an inherited breast or ovarian cancer are recommended to undergo 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 [51]. The incidence and prevalence of ovarian cancer makes consideration of a high false-positive rate very important when screening is planned. 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 cancer mortality and 15 % of women who had a false-positive result who underwent surgery had a serious complication [52]. The USPSTF, in their recommendation against routine screening, notes that screening may lead to patient harm, including from invasive procedures such as surgery [51].

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

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combination have not been demonstrated [53, 54]. ACOG recommends bilateral salpingo-oophorectomy by age 40 for risk reduction in women with BRCA 1 or BRCA 2 mutations[55]. 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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1 Introduction

Benign breast disease is a common occurrence in family medicine. Patients may present with masses, skin lesions, breast pain, breast feeding 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.

2 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.

3 History, Physical Exam, and Initial Workup

A patient may present with complaint 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.

3.1 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

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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]

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.

3.2 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 U.S. 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 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 [5].

3.3 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]. However, both ACOG and ACS recommend CBE every 1–3 years from ages 20 to 39 and annually after age 40 [8]. 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 54 % and 94 %, respectively [2].

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, conduct 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 [9].

3.4 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 [9]. Women under 30 should be evaluated with ultrasound due to increased sensitivity of detecting lesions in dense breast tissue [9]. 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 % 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 [10]. 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.

3.5 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 [11]. Ultrasound-guided CNB has

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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
6	Known biopsy-proven malignancy	n/a	Surgical excision when clinically appropriate

Adapted from Salzman et al. [9]

a sensitivity of 99 % for palpable lesions and 93 % for nonpalpable lesions [11]. 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 [12].

3.6 The Triple Test

The triple test includes clinical exam, imaging, and tissue sampling. When performed with concordant results, diagnostic accuracy approaches 100 % [11]. 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 [11]. An approach to management of palpable breast masses is summarized in Fig. 1.

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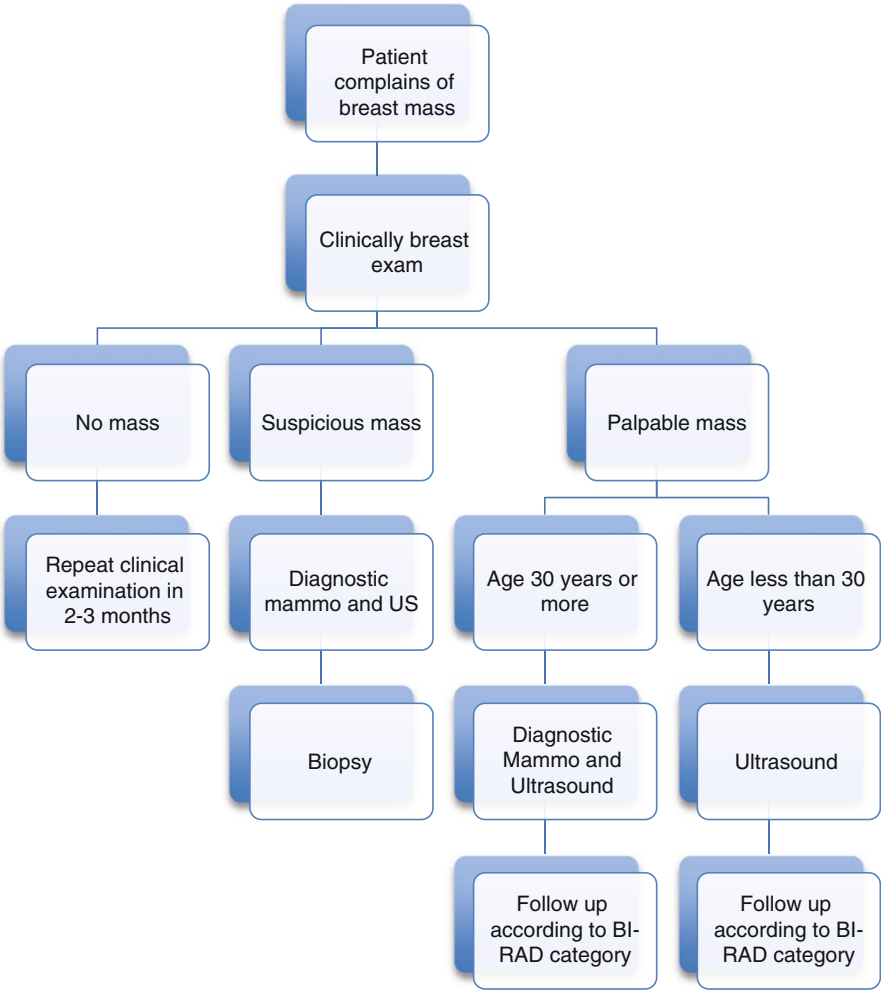

Fig. 1 Management of breast masses (Adapted from Neal et al. [12] and Pearlman and Griffin [13])

4 Common Chief Complaints

4.1 Breast Pain (Mastodynia/Mastalgia)

Breast pain makes up 66 % of breast complaints and can be categorized as cyclical (relating to menses) or noncyclical [9] (Table 3).

4.1.1 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 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 [15].

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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
Dietary changes
Decreasing dietary fat intake
Methylxanthine/caffeine reduction (coffee, tea, sodas, chocolate)
Vitamin E
Evening primrose oil
Soy
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
Gonadotropin-releasing hormone agonists

Adapted from Andolsek and Copeland [3] and National Comprehensive Cancer Network [14]

4.1.2 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 [15]. Cold or heat compresses and massage may also alleviate symptoms. One clinical trial 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. Evening primrose oil (gamma-linolenic acid), 3,000 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.

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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. 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 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.

Gestrinone, a synthetic 19-nor-testosterone 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) have not demonstrated clinical data for the treatment of mastalgia especially given their hypoestrogenic side effects; a decrease in bone mineral density is usually reversible.

4.2 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

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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.

4.2.1 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].

4.2.2 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].

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4.3 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 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 [9].

4.3.1 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 [16]. 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].

4.3.2 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.

4.3.3 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].

4.4 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 [17, 18]. 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 [18]. Early studies have shown that serum levels of estrogen, insulin, C-reactive protein, and adiponectin are independent

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risk factors for benign proliferative breast disease although investigation is needed [19]. 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, and red meat may lower risk of benign breast disease [20].

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 [21]. 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 [13]. 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, 9 out of 10 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.

4.4.1 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, 11]. 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 [13]. 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

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and diminish once menses start and are rare in postmenopausal 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 [13]. 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 [13].

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, 21]. 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 [22].

4.4.2 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 [13]. A single, central papilloma is benign and does not confer an increased risk for subsequent breast cancer. However, papillomatosis (at least five 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 [13].

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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 [13].

4.4.3 Atypical Hyperplasia

Atypical hyperplasia encompasses both atypical ductal hyperplasia (ADH) as well as atypical lobular hyperplasia (ALH). ADH confers up to fivefold increase in risk for subsequent breast cancer [13]. 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 months and annual mammograms [8]. 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 [13].

4.5 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 persist 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 is recommended. Overall, eighty percent of palpable breast masses present in pregnancy are benign [23].

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 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 [23]; see above for further details.

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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. [22]

4.6 Male Breast Conditions

4.6.1 Gynecomastia

Gynecomastia is the proliferation of glandular breast tissue in men due to disruption of the estrogen to progesterone ratio [24]. 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.

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 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 [25].

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Family Medicine
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Breast Cancer

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General Principles

Definition/Background

Except for skin cancer, **breast cancer** is the most common cancer in women worldwide [1], and it is the leading cause of cancer-related mortality, with almost 50 % of cases and nearly 60 % of deaths occurring in lower-income countries [1]. For women in the United States (USA), it is the most common cancer [2, 3], the second most common cause of cancer-related mortality, and the leading cause of cancer-related mortality in women age 20–59 [4]. Family physicians play an important role in screening, diagnosis, and follow-up of breast cancer patients and can be a valuable part of a multidisciplinary team approach [5–10].

Classification

Breast cancer is classified as either in situ or *invasive*. In situ breast carcinoma (CIS) is classified as either **ductal carcinoma in situ** (DCIS), the most frequent type, or **lobular carcinoma in situ** (LCIS). DCIS accounts for 20–25 % of newly diagnosed breast cancers in the USA [11] and is considered a neoplastic, non-obligate precursor of **invasive breast carcinoma** (IBC). Similar to IBC, DCIS treatment involves surgery, with possibly medical and/or radiation therapy. LCIS is not considered a precursor lesion at this time, but *is* associated with an increased long-term risk of bilateral IBC. LCIS is typically treated with follow-up observation. Invasive ductal carcinoma (no specific type), accounts for approximately 75–80 % of IBC, **lobular carcinoma** for about 10 %, with the remaining 10–15 % classified into special histologic types based on specific morphologic features [12].

Epidemiology

Approximately 43 % of IBC is diagnosed in women ≥65 years of age (median age 61) [13], and approximately 20 % in women <50 years of age. Approximately 72 % of breast cancer survivors are ≥age 60, with fewer than 10 % being <50 years of age [13]. A woman has a 1 in 8 (12.3 %) **lifetime risk** (LR) of developing breast cancer and a 1 in 37 (2.7 %) LR of dying from breast cancer [14, 15]. These are average risks, and individual risk will depend on individual risk factors. In January 2014, more than 3.1 million US women were living with IBC [13], with an estimated additional 232,670 and 58,000 new diagnoses of IBC and CIS expected that year, respectively [3, 4]. The LR of developing and dying from **male breast cancer** is 1 in 769 (0.13 %) and 1 in 3,333 (0.03 %), respectively [14, 15]. It is estimated that 2,240 new cases of male breast cancer (median age, 67) occurred in the USA in 2014, with approximately 410 men dying from breast cancer-related causes that year [4].

The **incidence** of IBC rose steadily among women of all age groups until 1985 and then stabilized until 1993. Between 1993 and 1999, in women ≥50 years of age, incidence rates increased again (remaining stable in women <50). The reason for this is not clear, but may be attributable to the prevalence of mammography screening, rising rates of obesity, and increased menopausal hormone use [3]. Subsequent changes in mammography screening rates and decreased use of menopausal hormones may at least partly

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explain the decline in IBC rates between 1999 and 2004. Since 2004, the incidence of IBC seems to have stabilized again for all women, estimated at 122.2 cases per 100,000 women [4]. Incidence of CIS also rose steadily through the 1980s, but unlike IBC, continued to rise until about 1999, particularly in women ≥50 years of age. As of 2014 [13], the incidence of CIS has generally stabilized in women ≥50 years and older, but continues to increase in women <50 years of age.

After slowly increasing for many years (0.4 % annually from 1975 to 1990), the **mortality** from breast cancer-related causes has improved over the last several years [13]. Death rates have decreased by 2.2 % per year from 1990 to 2007 for women of all ages combined, with a slightly larger decrease among women <50 years of age (3.2 % per year) compared to women ≥50 years of age (2.0 % per year). As of 2014, the mortality from breast cancer-related causes in the USA was 22.6 deaths per 100,000 women [4].

Approach to the Patient

Risk Factors

Improving breast cancer outcomes by early detection remains the cornerstone of breast cancer control [16, 17]. Family physicians are often the first point of contact for patients, particularly for lower-income patients, and particularly in rural areas [5]. As such, they play a critical role in the early detection of breast cancer. Fundamental history taking, although cliché, cannot be overstated [18, 19], as risk factors for cancer may be overlooked during a general history [20]. Identifying specific risk factors for breast cancer is critical in risk stratification for breast cancer screening. A previous history of breast cancer is important to elicit during the history, as it is a significant risk factor for developing a second breast cancer [1]. A family history is critical, because women who have a first-degree relative with breast cancer have almost twice the risk of getting breast cancer as women who have no affected relatives. This risk increases as the number of first degree relatives with breast cancer increases [1]. Approximately 5–10 % of breast cancers are due to germline mutations in breast cancer susceptibility genes, the most prevalent being the **BRCA**1/2 mutations. Women with a BRCA mutation have an increased LR (25–85 %) of developing breast cancer, depending on age and ethnic background [21, 22]. Genetic testing for a BRCA mutation should be considered in women with a personal or family history of breast or ovarian cancer (due to the relationship of the BRCA mutation with ovarian cancer), particularly if the cancer occurred at a young age. Surgical history of previous breast biopsy results (if any) is important, because a history of **atypical ductal hyperplasia** on previous biopsy caries an increased risk of developing breast cancer [23]. Being cognizant of the patients age is important, as the risk of developing breast cancer increases with age (more than 80 % of new diagnoses occur after age 50 [13]). A history of menarche and menopause should be taken. Early menarche and later onset of menopause are associated with an increased risk of breast cancer [1, 24]. Parity history should include age at first birth. Nulliparous women are at increased risk for development of breast cancer, and advanced age at first birth confers a relative risk for breast cancer greater than that of a nulliparous woman. A young age at first birth has an overall protective effect [1, 24]. **Hormone replacement therapy** (HRT) should be discussed, as information on HRT may be confusing to the lay person. The **Women's Health Initiative** (WHI) assessed the long-term effects of HRT in postmenopausal women and found an *increased* risk of breast cancer in women receiving combination HRT (estrogen plus progestin), compared to placebo [25]; however, the WHI estrogen alone trial showed a *decreased* risk for breast cancer in women with previous hysterectomy using estrogen only therapy [26]. More recent data suggests that combination HRT is an acceptable option for treatment of moderate to severe menopausal symptoms in women up to age 59, or within 10 years of menopause [27], and data continues to support that women with decreased risk factors for breast cancer who have a previous hysterectomy might be safely prescribed estrogen alone across all age groups [16, 28, 29].

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The family physician can be an integral part in clarification of these issues, which may result in additional treatment options for certain patients with postmenopausal symptoms. Ethnicity is another risk factor for breast cancer. African American women typically (1) present at an earlier age of onset (median age 54), (2) present at an earlier clinical stage, (3) have more aggressive pathology, and (4) have worse survival outcomes [4, 24]. Other possible increased risk factors for breast cancer which should be discussed include alcohol consumption, lack of physical activity, obesity, and history of radiation exposure [24].

Risk models including the Gail model [30, 31], Claus model [32], and others [33–36] may be helpful in quantifying an individual patients risk for breast cancer and may help to at least partially alleviate concerns in the anxious patient, as the perceived risk is often greater than the actual calculated estimate [37]. A thorough discussion on risk factors during initial and follow-up histories will help the family physician in appropriately directing the patient for screening and, if necessary, diagnostic evaluation.

Screening

Several organizations have made recommendations on screening guidelines [2, 38]. The three classic breast cancer screening tests are **breast self-examination** (BSE), **clinical breast examination** (CBE), and radiographic screening, typically with **mammography**. Several studies [37] have shown that BSE is likely to increase the chances of a woman detecting a benign breast lesion, without any reduction in cancer mortality. The American Cancer Society (ACS) suggests that it is "acceptable for women to choose not to do BSE, or to do BSE occasionally," [38] and currently no organization specifically recommends for a woman to perform BSE [2, 37].

The use of CBE continues to be generally supported by most organizations publishing screening guideline recommendations; however, guidelines differ depending on the organization [2, 38]. Several studies have suggested that the addition of CBE to mammography increases the number of cancers detected, because mammography may miss 10–15 % of palpable masses; however, screening with both CBE and mammography may result in a higher number of false-positive results, compared to women who have mammography alone [2, 37].

There is little debate that radiographic screening reduces rates of breast cancer mortality [2, 37]. There is general agreement that screening mammography should be offered to women 50–74 years of age; however, there are conflicting guidelines for screening women 40–49 years of age, and organizations differ on screening intervals [1, 2, 37]. As with BSE and CBE, screening mammography carries a risk of false-positive results. Estimates are that annual screening of women age 40–69 years of age will result in approximately 16 % of women undergoing unnecessary biopsies [37]. The **United States Preventative Task Force** (USPTF) and the **American Academy of Family Physicians** (AAFP) support routine *biennial* screening for women 50–74 years of age, based on a controversial study supported by the USPTF in 2009 [39]. This study argued two fundamental questions – should mammographic screening maximize (1) the number of breast cancer deaths prevented or (2) the number of years of life gained by early detection? The latter would result in a significant number of false-positive results, leading to unnecessary biopsies, without a significant reduction in breast cancer-associated mortality [37, 39]. The consensus decision within the USPTF was to support maximizing the number of breast cancer deaths prevented, resulting in a reduction in the amount of recommended screening. A recent update of the 2009 USPTF recommendations stated that the decision to have screening mammography for breast cancer in women <50 years of age "should be an individual one" taking into account "a woman's own situation and her values regarding specific benefits and harms."[40] The USPTF is currently in the process of once again updating their recommendations on breast cancer screening [40].

Screening controversies have created the greatest confusion for women with a LR for breast cancer diagnosis of <15 % (as defined by models that are largely dependent on family history), the largest group. Radiographic screening recommendations for a high (≥20 %) or moderate (15–20 %) LR of breast cancer

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diagnosis are less controversial or poorly defined, respectively. **Magnetic resonance imaging** (MRI) is recommended in women at high LR for breast cancer (Table 1) [41]. Ultrasound is not recommended for screening, but may be an option for those high-risk women who either cannot undergo MRI or demonstrate dense breast parenchyma by mammography [41].

What does this mean for the family physician counseling a patient on breast cancer screening? Breast cancer screening should be discussed in relation to the patient's risk factors, the comfort level of the patient and the physician, and the limitations of the physician**.** The patient should be counseled on the differences between **breast self-awareness** (the concept that a woman should know how her breasts normally look and feel, and be aware of changes) and the benefits and limitations of BSE (a step-by-step approach using a specific schedule to examine her breasts). The value of CBE should be discussed, acknowledging the possibility of finding a palpable lesion which may actually be benign. The value of screening mammography should be discussed in the same light, as approximately 1 in 10 women who have a screening mammogram will need further evaluation, and in most cases, additional testing will be negative for cancer [37, 42]. Certainly, women at increased risk for breast cancer should be considered for more aggressive screening. Ultimately the decision should be individualized, keeping the patient's life expectancy, functional status, and goals of care in mind [2, 42, 43].

Diagnosis

History and Physical Exam

Diagnostic evaluation starts with either a presenting complaint on history or an incidental finding on physical examination. After the estimated risk for breast cancer has been determined, the patient should be assessed for specific symptoms. *Any patient at high risk* for breast cancer presenting with *any* of the symptoms or signs below should be considered for referral to a subspecialist. Presenting symptoms specific to the breast include **breast pain**, **nipple discharge**, breast **asymmetry or thickening**, **changes in the breast skin** (color changes, nipple excoriation, eczema, ulcers), and a **palpable mass**. Breast pain without any other findings on physical exam is rarely a sign of carcinoma, and most women with carcinoma do not present with breast pain [44]. Careful history to elicit the duration and frequency of the pain is important, as cyclic breast pain may be related to menstrual cycling. Nipple discharge is also rarely a sign of carcinoma; however, the likelihood of nipple discharge being secondary to carcinoma does increase with age [44]. The physical exam can be helpful in determining if a nipple discharge warrants additional investigation. Most pathologic discharges contain blood and are unilateral and spontaneous. Non-spontaneous, bilateral, and/or non-bloody discharge in a women <40 should be reassured and observed and referred if symptoms persist. Non-spontaneous, bilateral, and/or non-bloody discharge in

Table 1 MRI breast screening recommendations[a]

BRCA mutation
First-degree relative of a BRCA carrier
≥20 % lifetime risk (LR) of breast cancer[b]
Radiation to chest between the ages of 10 and 30
Specific genetic syndromes, either in the patient or first-degree relative
Li-Fraumeni
Cowden
Bannayan-Riley Ruvalcaba

[a]Adapted from Mainiero et al. [41]
[b]As defined by models that are largely dependent on family history

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a women ≥40 warrants a referral for diagnostic mammogram, with appropriate follow-up. *Any* spontaneous or bloody discharge warrants referral to a subspecialist. Breast asymmetry, thickening, or skin changes should be referred to a subspecialist for consultation, with consideration for diagnostic imaging. Women presenting with a breast mass should be promptly considered for diagnostic imaging but reassured until a final diagnosis is made by the radiologist, as normal structures mistaken for a mass include a prominent rib or costochondral junction, the normal glandular nodularity of the premenopausal breast, the inframammary ridge, or a firm margin at the edge of a previous biopsy site [44]. Suspicious masses tend to be hard, firm, and/or fixed, with irregular borders. Benign masses tend to be more mobile, with more well-demarcated borders. General malaise, bony pain, and weight loss, while not specific for breast cancer, may be other symptoms that women with breast cancer present with, and should prompt additional investigation by the family physician, particularly in women at high risk for breast cancer.

Laboratory and Imaging

The **assessment categories for mammographic evaluation** are outlined in Table 2.

Workup of a suspicious presentation should be tailored to the patients' age and the physician's index of suspicion. Breast asymmetry, breast thickening, breast skin changes, non-spontaneous bilateral non-bloody nipple discharge (women ≥40), any spontaneous bloody nipple discharge, and any palpable breast mass all warrant consideration for diagnostic imaging and appropriate follow-up. For women <30, ultrasound ± diagnostic mammogram is typically recommended (except for skin changes, in which case diagnostic mammogram ± ultrasound is recommended). For women ≥30, diagnostic mammogram ± ultrasound is recommended [44]. Subsequent follow-up is based on the diagnostic imaging findings (Table 3). For all clinical presentations, *any* increase in clinical suspicion should warrant referral. In *any* patient in whom return visits are unsure, or in the extremely anxious patient, referral to a subspecialist with adequate documentation is recommended [43].

Biopsy

A definitive diagnosis of breast cancer is obtained through tissue sampling (needle aspiration, needle core biopsy, or excisional biopsy) by the treating surgeon. The final diagnosis is made by the pathologist. If breast cancer is diagnosed, additional laboratory studies may be requested in preparation for post-biopsy consultations. Several of these studies can be done by the family physician (CBC, liver enzymes, and alkaline phosphatase) at a post-biopsy office visit, reinforcing the family physician as a part of the multidisciplinary treatment team. Other studies may be required, including a bone scan, computed tomography (CT) scan, MRI, or positron emissions tomography (PET) scans. Genetics and fertility

Table 2 Breast Imaging-Reporting and Data System (BI-RADS) categories[a]

BI-RADS category	CATEGORY ASSESMENT
0	Needs additional imaging evaluation
1	Negative
2	Benign finding
3	Probably benign finding
4	Suspicious abnormality
5	Highly suspicious of malignancy
6	Known biopsy-proven malignancy[b]

[a]Adapted from National Comprehensive Cancer Network [44]

[b]This category is reserved for examination *after* biopsy proof of malignancy, in which there are no other known mammographic abnormalities other than the known cancer that might need additional evaluation

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Table 3 Follow-up for concerning clinical presentations and radiographic findings[a]

	BI-RADS category				
Clinical presentation	1	2	3	4	5
Breast asymmetry/thickening	Observe[b]			Refer for consultation	
Breast skin changes	Refer for consultation regarding diagnostic imaging[c]				
Non-spontaneous discharge	Observe[d]		Observe[e]	Refer for consultation	
Spontaneous discharge	Refer for consultation regarding diagnostic imaging[c]				
Palpable mass (<30 years old)	Observe[f]		Refer for consultation		
Palpable mass (≥30 years old)	Refer for consultation	Observe[g]	Refer for consultation		

[a]Adapted from National Comprehensive Cancer Network [44]
[b]Physical exam every 3–6 months and repeat diagnostic imaging every 6–12 months for 2–3 years
[c]Surgical consultation prior to deciding on the need for and type of diagnostic imaging
[d]Follow normal screening recommendations
[e]Repeat diagnostic imaging at 6 months, and then every 6–12 months for 2–3 years, if clinical suspicion is low and the discharge is stable or resolving
[f]Repeat diagnostic imaging every 3–6 month for 1–2 years if clinical suspicion is low and the patient has a negative ultrasound or if the mass is a simple cyst
[g]Anything other than a simple cyst, BI-RADS category 2 should be referred for further follow-up (including a negative ultrasound or a BI-RADS category 1 finding)

counseling may be a consideration. Decisions on these additional studies and counseling should always be considered in consultation with the treating surgeon, medical oncologist and radiation oncologist [45].

Treatment

Familiarity with staging and various treatment options makes the family physician a valuable resource to the patient during this difficult time period, again reinforcing the family physician's role as part of the multidisciplinary treatment team.

Staging

After the diagnosis of breast cancer is made, the patient is clinically staged. Staging takes into account clinical, radiologic, and pathologic information, including tumor size, and the presence and extent of both lymph node involvement and metastatic disease to non-nodal tissue [46]. Along with other clinically significant **prognostic factors** (Table 4) staging helps to dictate treatment options, including neoadjuvant chemotherapy, which may reduce the stage and increase the possibility of the patient receiving **breast conserving therapy** (BCT) [1, 46].

Surgery

In 2011, approximately 59 % of women with earlier stage (stage 0–2) breast cancer were candidates for and chose some combination of BCT (as opposed to mastectomy) with or without radiation and /or chemotherapy [3]. This option is less available to women with later stages (stages 3 and 4) of breast cancers. In 2011, approximately 59 % of women with later stages of breast cancer received some combination of mastectomy with or without radiation and/or chemotherapy [3]. Approximately 1 % of women with earlier stage cancer, and approximately 10 % of women with later stage cancer, opted not to have any treatment in 2011 [3], a decision the physician should be prepared to discuss with the patient.

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Table 4 Clinically significant prognostic factors in breast cancer[a]

Clinical stage
Tumor grade
Hormone receptor status (ER, PR)
Her-2 status
Paget's disease
Circulating tumor cells (blood)
Disseminated tumor cells (bone marrow)
Multigene signature scores (i.e., Oncotype Dx®)

[a]Adapted from Edge et al. [50]

Radiation

Radiation therapy can be administered locally to the chest wall, regionally based on lymph node distribution and involvement, to part of the breast (partial breast), or to the whole breast (whole breast). The decision as to which type of radiation should be given is made by the radiation oncologist in collaboration with the treating surgeon and medical oncologist, based on the type of mastectomy (partial vs. total), tumor characteristics, margin status, and the presence and extent of lymph node involvement. Although radiation therapy has not been shown to affect survival [1, 46], it has been shown to decrease local **recurrence** by approximately 50 %. Seventy percent of all recurrences occur within 5 years [1, 47]. Risk factors for local recurrence include positive margins, young age, hormone receptor status, larger tumor size, positive nodes, and lymphovascular invasion [1].

Adjuvant Hormonal and Systemic Chemotherapy

Chemotherapy has also been shown to reduce the risk of local recurrence [1]. Current guidelines for adjuvant **hormonal** and **systemic** chemotherapy treatment for IBC vary depending on **estrogen receptor** (ER), **progesterone receptor** (PR), and **human epidermal growth factor receptor-2** (HER-2) expression [1, 46]. The decision as to which type(s) of therapy given is made by the medical oncologist in collaboration with the treating surgeon and radiation oncologist. Hormonal therapy is given for patients with ER- or PR-positive disease, with consideration for menopausal status. For premenopausal women, **tamoxifen** is typically given for at least 5 years, with consideration for ovarian ablation or suppression. For postmenopausal women some combination of an **aromatase inhibitor** and tamoxifen is typically given, with the use of only a single agent at a time, for at least 5 years. Typical systemic chemotherapy regimens for breast cancer will include doxorubicin/cyclophosphamide followed by paxitaxel, either weekly or every two weeks. **Trastuzumab** ± pertuzumab is added for Her-2 positive disease [46]. Multiple other systemic chemotherapy regimens exist. Patients on systemic chemotherapy require periodic cardiac monitoring, and this can be provided by the family physician in coordination with subspecialty consultation. Patients may present to the family physician with a variety of **side effects**. It is helpful to have contact information for all subspecialists on the multidisciplinary team, in case consultation is required for chemotherapy side effects.

Breast Reconstruction

Breast reconstruction is an optional procedure that has been associated with an improved quality of life for many patients. It is typically discussed with the treating surgeon in consultation with plastic surgery, prior to the initial surgery. Reconstruction is adapted to the patient's individual clinical situation including plans regarding radiation, comorbid disease, body habitus, and smoking status. The family physician can play an integral role in co-management of these latter three considerations. Reconstruction options

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include breast implants and/or autologous tissue transplantation (donor tissue taken from another body site such as the abdomen, back, buttocks, or thigh) and typically require a series of procedures: (1) the initial reconstruction (which may occur at the time of the mastectomy or at some point in the future), (2) subsequent surgery on the contralateral breast to improve symmetry, (3) possible revision surgery involving the breast implant or donor tissue site, and finally (4) nipple and areola reconstruction with tattoo pigmentation [46].

Follow-Up Care

Several randomized studies have suggested that in patients with early stage breast cancer, when **follow-up** care is delivered by a family physician compared with **specialist-led follow-up**: (1) there are no differences in **recurrence**-related serious clinical events; (2) there are no differences in health-related quality of life; (3) that patients may be more satisfied; and (4) that overall health-care costs might be decreased [8, 12, 48, 49]. Research has also shown that most recurrences are detected by patients during the intervals between routine follow-up visits [12]. These patients may present to the family physician first. In addition, frequently patients will present to their family physician – not to their specialist – for psychosocial complaints (the most common issue raised during follow-ups [8]) and complaints about posttreatment **side effects** [12]. In women who undergo surgery with radiation, **lymphedema** can be a long-term side effect, if the patient also had either a sentinel lymph node biopsy and/or axillary node dissection (6 % and 20 % incidence of lymphedema, respectively). Other long-term side effects with radiation include numbness, tingling, or tightness in the chest wall, arms, or shoulders. Between 25 % and 60 % of women develop chronic pain. Treatment with **chemotherapy** can lead to impaired fertility and premature menopause (which increase the risk of osteoporosis) as well as cardiomyopathy and congestive heart failure (anthracyclines and HER-2-targeted drugs). Treatment with **aromatase inhibitors** can also cause osteoporosis, as well as myalgia and arthralgia. Treatment with **tamoxifen** can cause postmenopausal symptoms. Patients with breast cancer may also experience cognitive impairments and chronic fatigue [46]. While these complaints may be directly related to posttreatment side effects, some may be warning signs of **recurrence**. *Any* suspicion for recurrence should be immediately referred to the subspecialist for additional evaluation. Certain patients are more appropriate for **specialist-led follow-up** including later stage patients, patients treated with adjuvant hormonal therapy with a planned switch to an alternative agent after 2 or 5 years, high risk of early relapse, significant recurrence-related anxiety, and a history of poor compliance with treatment and/or follow-up [12].

Prognosis

Clinically significant prognostic factors are shown in Table 4. Stage is the single most influential prognostic factor for breast cancer survival [46, 50]. The overall 5 year –**relative survival rate** (RSR) – for women with breast cancer is approximately 89 % for all races, with a noticeably lower 5-year RSR for African American women (79 %) [4]. Localized (stage 0–1) breast cancer has a significantly better 5-year RSR (99 %) compared to regional (84 %) and distant-stage (24 %) breast cancer, reiterating the importance of early detection [4, 46, 50]. Regrettably, only 61 % of breast cancers (52 % for African American women) are diagnosed at the local stage [4]. Continued education, focus on breast cancer risks, and proper screening will hopefully increase the number of women who are diagnosed at an earlier stage.

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Conclusion

There is ample evidence supporting the role of the family physician in the care of patients at risk for and those who have been diagnosed with breast cancer [5, 7–10, 23, 48, 49]. The patient's history, including risk factors for breast cancer, is critical in directing the patient for appropriate screening. The family physician can be valuable part of the multidisciplinary team caring for the breast cancer patient, providing first-line support, evaluation of posttreatment side effects, and early referral for suspected recurrences.

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Selected Disorders of the Female Reproductive System

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Acute Pelvic Pain in Women

Background

Pelvic pain is a common complaint in both the acute and primary care settings. The differential is broad and is dependent upon the patient's age and whether or not she is pregnant. Aside from reproductive etiologies, genitourinary, gastrointestinal, and musculoskeletal causes must also be considered [1]. Acute pelvic pain has been defined as pain lasting less than 48 h, whereas chronic pelvic pain has been present for at least 6 months [2]. This section will specifically focus on acute pelvic pain with an emphasis on an evidence-based approach using clinical history and physical examination skills.

History

Just as with any patient that enters an exam room, the key to the evaluation of pelvic pain lies within the physician's ability to take a thorough and accurate history. The patient should be asked about the quality, intensity, location, timing, duration, radiation, and 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 LMP, sexual partners, and history of sexually transmitted infections [3].

Physical Exam

An important step in evaluating pelvic pain, is the ability to assess the severity of the woman's condition. First, look at her vital signs. Fever is an indication of an inflammatory process, such as infection Hypotension may be a sign of hemorrhage, such as with a ruptured ectopic pregnancy or a hemorrhagic cyst. Next, assess the patient's general appearance. Is she well appearing, toxic, or something in between?

The clinician must then determine if the woman's symptoms are from an abdominal or pelvic source, which can be done through physical exam. The key to an appropriate abdominal examination is assessing for signs of peritoneal irritation. This is confirmed by 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. A speculum examination is necessary to visualize the cervix and vagina [3]. If discharge is present, it should be noted and sampled for further evaluation. Gonorrhea and chlamydia testing would also be warranted at this time. The cervix should be palpated through bimanual exam, taking note of its position and for any tenderness. With the other hand, press down on the lower abdominal wall to assess the uterus for tenderness or masses. There are definite limitations to pelvic examination to include experience of 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 quickly 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 woman [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 upon physical exam and history findings. Leukocytosis may be seen in PID, appendicitis, and pyelonephritis, and thus if suspected, obtain a CBC. Studies have found that only 60 % of women with PID have an elevated serum white blood cell count, which is only of value if elevated [9]. Erythrocyte sedimentation rate (ESR), a non-specific inflammatory marker, may be elevated in PID and ectopic pregnancy, so could be considered. In the pregnant patient, Rh testing is performed if there is concern for threatened abortion [4]. Urinalysis and culture is when 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 causes 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 a 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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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 × 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

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 general endometritis typically include pelvic pain, general malaise, abnormal vaginal discharge, bleeding [14]. Postpartum endometritis is associated with fundal tenderness and foul-smelling vaginal discharge. Acutely, neutrophils may be seen on wet prep and the patient may have a fever. 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 a reported association between bacterial vaginosis and endometritis [15].

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 [16]. The CDC recommends empiric treatment for PID in sexually active women if they are experiencing pelvic or lower abdominal pain if no cause identified for illness other than PID, and if the patient has 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. gonorrhea* or *C. trachomatis*. The recommended outpatient treatment is 250 mg of IM ceftriaxone in a single dose

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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 [15].

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 is generally advised in a woman with signs of sepsis. Women without signs of hemodynamic instability and an abscess less than 9 cm in diameter and are premenopausal are candidates for antibiotic therapy alone [17]. Antibiotic therapy should include coverage for sexually transmitted pathogens (*N. gonorrhea* and *C. trachomatis*) as well as anaerobes. The CDC recommends a minimum of 2 weeks of antibiotic treatment and close follow-up is necessary if outpatient treatment is being considered [15].

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 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 increased uterine mobility, adnexal masses, or uterosacral nodularity. The pain of endometriosis is typically cyclic and may be associated with dyspareunia, dysuria, and dyschezia. Adenomyosis is also 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 [18].

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 managed 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 [19].

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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 features associated with torsion may be nonspecific. The patient typically presents with acute onset abdominal pain, within the past 24 h. 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 of the involved adnexa is often seen in those individuals with abnormal Doppler findings. 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 [20].

Nongynecologic Causes of Acute Abdominal Pain

Gastrointestinal

Appendicitis is the most common cause of 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 and 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 [16].

Conclusion

In the evaluation of acute pelvic pain, the clinician must first rule out the emergent, life-threatening conditions. Given the broad differential, a thorough and complete history, physical examination, and urine pregnancy test are indicated in every patient presenting with pelvic pain. Your clinical judgment should then lead you to order the appropriate labs and imaging as discussed above to arrive at the correct diagnosis.

Pelvic Pain in Men

Women are not the only sufferers of pelvic pain; however, the differential between men and women presenting for pelvic pain varies vastly. The nongynecologic causes as discussed above should be considered in both men and women reporting pelvic pain.

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Table 2 Diagnosis of Toxic Shock is based on the presence of two majorcriteria, 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 Mucous membrane: oral, vaginal, conjunctival **Hypotension** (systolic BP < 90)	**CNS**: Altered mental status w/o focal deficit **Cardiovascular**: Distributive shock, arrhythmia, non-specific ST wave EKG changes, heart failure **Pulmonary:** Pulmonary edema, respiratory distress syndrome **Gastrointestinal:** Nausea, vomiting, 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 prostatitis/chronic pelvic pain syndrome (CP/CPPS) presents as lower abdominal (pelvic) pain and/or urologic symptoms. The National Institutes of Health (NIH) has classified this syndrome into four categories. Acute bacterial prostatitis (category I) is characterized by acute illness, urinary tract infection symptoms, pelvic pain, and cloudy urine. Patients with chronic bacterial prostatitis (category II) typically present with recurrent symptoms of urinary tract infection with repeated isolation of the same urinary pathogen [21]. CP/CPPS can be further subdivided into inflammatory versus noninflammatory causes, although the symptoms are generally the same. Common presentation includes pain (pelvic, low abdomen, urinary, testicles, and perineum, with ejaculation), difficulty with urination, and at times hematospermia [22].

All men should undergo a urinalysis with culture initially. Gonorrhea and chlamydia testing should be obtained if suspicion, based on sexual history. Diagnostic imaging may be pursued on a case-by-case basis, dependent upon symptoms at presentation. CT scan is considered if abdominal pain is present, whereas ultrasound is the imaging of choice when testicular pain is the chief complaint. Bladder ultrasound and measurement of post-void residual volume is considered with symptoms of incomplete emptying [23].

Alpha-blockers are often prescribed for men with CP/CPPS, although there is lack of substantial evidence to support their use. Alpha-blockers are; however, known to improve lower urinary symptoms, which may also be found in benign prostatic hyperplasia in addition to CP/CPPS. Alpha receptors are located within the central nervous system; thus, blockade has been implicated in reduction of pain in long-term pain syndrome. Alpha-blockers may also reduce inflammation of the lower urinary tract, which has been implicated as one of the causes of CPPS [24].

Toxic Shock Syndrome

Toxic shock syndrome (TSS) was a highly researched topic in the 1980s and after numerous cases was documented associated with higher absorbancy tampons. The incidence of TSS has declined after some of the brands of tampons were discontinued [25]. 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 symptoms including fever (temperature greater than 102), diffuse macular erythroderma, desquamation (1–2 weeks after onset of rash), hypotension, and multisystem involvement involving three or more organ systems [26]. Abscesses, cellulitis, bursitis, postpartum infections, postsurgical procedures, vaginal infections, and intrauterine devices have been associated with TSS [25] (Table 2).

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Chronic Pelvic Pain

Background

Chronic pelvic pain (CPP) is defined as a non-menstrual, noncyclical pelvic pain that has been present for at least 6 months, not related to cancer, severe enough to interfere with daily activities, often requiring medical or surgical intervention and treatment [27–34]. Reported prevalence rates range from 3.8 % to 24 % in women aged 15–73 years [34], roughly 15 % of the female population [35]. Pelvic pain accounts for up to 39 % of primary care visits [34] and is the single most common indication for referral to gynecology [36]. CPP accounts for up to 20 % of secondary care appointments [37]. In the United States, direct and indirect health-care costs exceed two billion dollars a year [34, 36]. CPP is often associated with negative behavioral, cognitive, sexual, and emotional consequences [38], as well as increased drug and alcohol use and abortion [29, 34]. 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 [28, 30–32, 35, 39].

The pathophysiology of CPP is poorly understood [40, 41] and is often multifactorial. CPP is rarely found to be due to a single cause [36]. Up to 60 % of patients will not receive a diagnosis for their CPP [34, 35]. Symptoms are often suggestive of urinary tract, gastrointestinal, pelvic floor, or gynecological sources [37]. 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 [28, 30–32, 39–41].

History

As with any patient in the primary care setting, history taken from the patient regarding her pain is of utmost importance. A full review of systems is indicated [35], as is a full history of previous work-up for the pain, including all surgical and nonsurgical diagnostic approaches [28, 35]. It is important also to discuss with the patient how her CPP affects her daily activities and sexual function and satisfaction. Treatments tried in the past, both that provided relief and those that did not, are helpful in teasing out the next steps in both diagnosis and management [28].

A discussion with the patient regarding her pain, in terms of character, quality, intensity, radiation, and causative and alleviating factors, should occur [35]. It is important for the provider to differentiate between visceral and somatic pain when taking a history. Visceral pain is typically reported as dull, crampy, and poorly localized and can be associated with nausea, vomiting, and sweating due to autonomic feedback [35]. 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 [35].

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 [28], and chaperones should always be present, with at least one person of the medical team being female [35]. The exam should begin with a gait analysis [31, 32, 34, 35], paying attention to her movement and of her sitting pose. Heart and lung exam, as well as appropriate HEENT exam, should also be part of this comprehensive evaluation. Upon evaluation of her abdomen, listen for bowel sounds in each quadrant. She should then be inspected for scars of her abdominal wall, masses in her abdomen, tenderness, as well as rebound or fluid shifting [31, 32, 34, 35].

A pelvic exam should be performed last and should be performed after the patient voids [34]. First, inspection of the tissues of the external genitalia is key, to note discoloration, scarring, or signs of dermatologic or infectious processes [35]. A moist cotton swab can be used to determine any point

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tenderness of the external structures [28]. A gentle digital exam can help determine if there is pelvic floor weakness, spasms, and tenderness [28, 31, 32, 34, 35]. 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 [35]. It is important to note the appearance of the cervix and if there is discharge present [34, 35]. 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 [28, 34, 35].

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 [35]. Colonoscopy may be warranted if the patient has a report of hematochezia or is greater than 50 [28].

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 [31, 32]. 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 [31, 32].

Labs and Imaging

Due to the multifactorial etiology and pathophysiology of the source of pelvic pain [37, 35], a six-point system has been developed to assist the physician in guiding the work-up. Named "UPOINT," it consists of recommendations for *u*rinary, *p*sychological, *o*rgan specific, *i*nfectious, *n*eurological, and *t*ender musculature causes [37]:

- *Urological*: assess urine flow and voiding diary; consider cystoscopy, ultrasound, and flowmetry
- *Psychological*: assess for depression, history of abuse, pregnancy losses, coping mechanisms (catastrophizing), 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 neuro 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

Specifically, 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 processes, such as inflammatory bowel disease or antitissue transglutaminase antibody tests for celiac disease [28].

Imaging commonly performed includes a pelvic ultrasound, to evaluate the bladder, uterus, and ovarian structures [29]. Transvaginal ultrasound is more sensitive to evaluate for pelvic masses and adenomyosis than transabdominal scanning [31, 32]. 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 [35]. MRI is useful for characterizing pelvic masses and is the imaging modality of choice for diagnosing adenomyosis [31, 32]. Laparoscopy, cystoscopy, and hysteroscopy allow direct visualization of the involved structures and can also be useful for the evaluation of CPP [28, 29, 34, 35].

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Diagnosis and Management

The four most common causes of CPP include endometriosis, adhesions (intra-abdominal/intrapelvic), interstitial cystitis, and irritable bowel syndrome [28, 35].

Several organs and organ systems have been implicated in the cause of CPP [37, 42]:

- 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
- Intermittent chronic anal pain
- Pelvic bone stress fracture

The most common cause of chronic pelvic pain is endometriosis [35], defined as the presence of endometrial tissue outside of the endometrial cavity [31, 32, 35]. 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 [29, 31, 32, 36]. 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 [31, 32]. 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 [31, 32]. Adhesions can arise from chronic pelvic inflammatory disease, prior surgery, endometriosis, or unknown factors [31, 32]. 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 [31, 32]. Uterine fibroids are associated with pain, dysmenorrhea, pressure, and menorrhagia [31, 32].

Interstitial cystitis is a nongynecological source of CPP that is manifested by bladder pain, urinary frequency, urgency, or nocturia. Pain is often suprapubic [31, 32, 35, 37]. 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 [37, 43]. Childbirth, surgery, bacterial infections, instrumentation, or autoimmune processes are considered possible insults contributing to bladder pain syndrome [37]. After initial evaluation to rule out infection, voiding diaries can help with diagnosis and to monitor treatment [28]. Cystoscopy to perform intravesical potassium sensitivity testing has a specificity of 83 % and sensitivity of 73 % [28].

Irritable bowel syndrome is the chronic presence of abdominal pain three or more days a month, associated with changes in stool frequency or form (loose vs. solid) [35]. 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 [35].

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Treatments

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 [28] and in a tertiary center equipped and experienced for management of chronic pain [39]. Selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) have level III evidence in treatment of refractory pain [28].

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 [31, 32]. The theory is that CPP that varies with menstrual cycling will respond to the suppression of the hypothalamic-pituitary-gonadal axis [28].

NSAIDs are the first-line therapy for interstitial cystitis, although studies have not found NSAIDs or opioids to be routinely effective [35]. Pentosan polysulfate sodium (PPS) is approved by the FDA for treatment of IC and is thought to mimic the normal glycosaminoglycan layer that protects the urothelium that is dysfunctional in IC [35, 43]. Treatment may require up to 6 months to be effective, but is effective in up to 32 % of patients [28, 31, 32, 35]. Dietary modifications have also been suggested in the treatment of IC, such as elimination of foods suspected to aggravate the urothelium, including caffeine, alcohol, spicy and acidic foods, artificial sweeteners, and carbonated beverages [28].

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 [35].

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 [34]. 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 [39].

Hysterectomy may be indicated in the treatment of CPP and up to 18 % of hysterectomies are performed for CPP [39]. Hysterectomy is an acceptable treatment for endometriosis, adenomyosis, and uterine fibroids [31, 32].

Adhesion lysis was not found to be beneficial except in the setting of severe adhesions [40, 41].

Hydrodistention of the bladder by urogynecologists with intravesical instillations with dimethyl sulfoxide or bacille Calmette-Guérin has been shown to decrease pain for IC (2).

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 treatment requires a positive patient-provider relationship. First-line medications indicated for treatment of CPP include NSAIDs and hormone therapy

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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.

Endometriosis

First described over 150 years ago by Rokitansky [44], endometriosis is a disease that is defined by the presence of endometrial tissue found outside of the uterus, such as on the ovaries, on the fallopian tubes, inside the peritoneal cavity, inside the posterior cul-de-sac, and on the bowel; lesions have even been noted in the lungs, the brain, and bones and on or in the skin [44–46]. Primary symptoms reported are pain, increased menstrual flow, and infertility [44–46]. An estimated 10–15 % of all reproductive aged women suffer from endometriosis [44–46]. Up to one-third of patients undergoing evaluation for pelvic pain are found to have endometriosis, with 40 % of infertile women being found to have the disease [47]. Risk factors identified for endometriosis include first-degree relative with endometriosis, early menarche, late menopause, low BMI, Müllerian anomalies, nulliparity, prolonged menses (>5 days), and shorter lactation intervals. Pathogenesis of endometriosis is thought to be multifactorial. In the 1920s, Sampson proposed retrograde menstruation, a theory that continues to be the most widely accepted [45]. It is theorized that endometrial tissue can be transported in a retrograde fashion through the fallopian tubes into the peritoneal cavity [45] and can implant onto other structures. This theory is supported by a study that found menstrual blood in the peritoneal fluid in 90 % of healthy women evaluated at the time of their menses [46].

Another theory suggested in the 1960s by Ferguson is that of coelomic metaplasia, which is related to the theory that the peritoneum contains undifferentiated cells [45]. This theory suggests the transformation of normal peritoneal tissue into endometrial tissue, under the influence of endogenous stimuli such as hormonal or immunological factors to promote the differentiation of cells into endometrial cells [46].

The theory of benign metastasis suggests through lymphatic or hematogenous spread endometrial cells can lead to ectopic endometrial implants and endometriosis is established [45, 46]. It is this theory that is supported by findings of endometrial lesions found in the bone, lungs, and brain [46].

In the setting of the endometrial cells in abnormal locations, appropriate conditions also must be present for them to continue to survive and proliferate. Several processes have been studied and suggested. First, cell-mediated immunity is thought to be impaired in women with endometriosis, thus preventing clearance of the refluxed or otherwise traveled endometrial cells and fragments [45]. Leukocytes do not recognize the endometrial cells as abnormal in location and are thought to be resistant to lysis by the natural killer cells [46]. After the endometrial tissue implants, the immune system is further thought to potentiate the disease. This is thought to occur by increased numbers of leukocytes, macrophages, and cytokines in the peritoneal fluid, leading to inflammation, recruitment of capillaries, and ultimate proliferation of vascular supply to support the endometrial implants. Upregulation of tumor necrosis factor-α (TNF-α) and interleukin-8 (IL-8) in women with endometriosis promotes this proliferation and adhesion of endometrial implants, and local increase in cytokines may help facilitate neovascularization. The expression of vascular endothelial growth factor (VEGF) is found in high concentrations in the peritoneal fluid of women with endometriosis and correlates with the stage of the disease [46].

The inflammatory nature of endometriosis is due to the increased number of macrophages found in the peritoneal fluid. A unique protein similar to haptoglobin was identified from the peritoneal fluid of women with endometriosis, which was found to bind to the macrophages, limit their phagocytic capacity, increase their production of interleukin-6 (IL-6), and positively impact inflammation. Further, the peritoneal fluid

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in women with endometriosis is rich in prostaglandins, and together these processes are thought to contribute to the pain and infertility experienced by patients [46].

Endometriosis affects fertility in up to 40 % of women [47], with an estimated 50 % of women with endometriosis suffering from infertility [44]. As previously discussed, endometriosis is associated with inflammation in the peritoneum. This inflammation is thought to alter ovulation and appropriate oocyte formation [45]. Additionally, the luteal phase is disrupted, likely a result of dysregulation of the progesterone receptors. The inflammatory effects also impact sperm motility, limiting ability of the sperm to fertilize the oocyte. Further, the inflammation can have toxic effects on the embryo and cause implantation failure [45]. Adhesions can develop due to the inflammation processes and lead to poor tubal function, tubal motility, disordered myometrial contractions [45], and ectopic pregnancy.

Treatment of Endometriosis

NSAIDs are considered first-line therapy for treatment of pain associated with endometriosis, but there is inconclusive evidence regarding effectiveness in relieving pelvic pain [47]. NSAIDs work by blocking the activity of COX-1 and COX-2 enzymes, inhibiting prostaglandin production, and inducing apoptosis of ectopic endometrial cells. This is despite the evidence that COX-2 activity has been demonstrated in high concentrations from the ectopic endometrial cells, as well as high levels of prostaglandins in the peritoneal fluid of patients with endometriosis. The side effect profile for NSAID use includes peptic ulcer disease, increased bleeding risk, and anovulation [47].

OCPs are also considered first-line therapy. Their mechanism of action is inhibition of gonadal estrogen, suppressing ovarian activity, reducing estrogen-induced production of prostaglandins, and decreasing inflammation [47]. Best results have been demonstrated with continuous use OCP or those that allow for shorter duration of days off (4 vs. 7) with the placebo pills in a pill pack, limiting the recovery phase of estrogen synthesis. Limitations in OCP use for treatment of endometriosis include desired fertility, increased thromboembolic events in smokers and women aged 35 or older, and quick return of disease state upon cessation of treatment [47].

Other hormonal treatments have been explored in the treatment of endometriosis. Progestins, GnRH analogues, GnRH antagonists, and selective estrogen receptor modulators are a few that have been studied. Progestins work by blocking central and peripheral mechanisms, leading to less mitogenic action and estrogen-induced proliferation of the endometrial tissues. The endometrium becomes atrophic and creates a pseudopregnancy state. A Cochrane review found that 100 mg/day of medroxyprogesterone acetate (MPA) is effective in control of pain; side effects of this include menstrual irregularities, weight gain, and breast tenderness. The levonorgestrel-releasing IUD has been used to treat endometriosis of the rectovaginal septum, providing relief in dysmenorrhea, dyspareunia, pelvic pain, and the size of endometrial implants. Similarly, Implanon (depomedroxyprogesterone acetate) has been seen to decrease pelvic pain in patients with endometriosis. Norethisterone acetate (NETA) causes hypoestrogenism by gonadotropin suppression and ovulation inhibition, leading to development of amenorrhea and atrophy of the endometrium. NETA has been found to help reduce pelvic pain in women with endometriosis and has a positive effect on calcium metabolism. More specifically, a prospective study found that NETA provided relief in women with colorectal endometriosis after 12 months of therapy. Danazol, a synthetic androgen derivative of 17α-ethinyltestosterone, was introduced over 30 years ago for the treatment of endometriosis and works by inducing a hypoestrogenic-hyperandrogenic state which significantly limits endometrial growth. Due to the high androgen levels, side effects such as weight gain, muscle cramps, acne, seborrhea, decreased breast size, hirsutism, and deepened voice have been reported. Gestrinone, a synthetic trienic 19-norsteroid, works by inhibiting the pituitary gland and release of gonadotropins, resulting in ovarian suppression and atrophy of the endometrium and endometrial implants. Although pain is reduced effectively, its use is limited by the anabolic and androgenic side effects [47].

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Table 3 Treatment options for Endometriosis

Medication	Mechanism of action	Effects	Side effects
OCP	Inhibits gonadal estrogen via negative feedback Suppresses ovarian function Reduction in estrogen-induced prostaglandins	Endometrial tissue growth suppressed Protects bone density	Increased thromboembolic events in smokers and women >35 years
NSAIDs	Decreases COX-2 activity Inhibits prostaglandin production Blocks growth of ectopic endometrial cells Induces apoptosis	No sufficient clinical data to prove as effective treatment for pelvic pain associated with endometriosis	Peptic ulcer Anovulation Bleeding risk
Progestins DMPA IUD Nexplanon/ Implanon NETA Danazol Gestrione	Reduces endometrial proliferation Creates pseudo pregnancy state Causes hypoestrogenism Suppresses gonadotropins Inhibits ovulation	Reduction of dysmenorrhea, pelvic pain, and dyspareunia Decreases size of implants Positive effect on calcium metabolism	Menstrual irregularity Breast tenderness Amenorrhea Weight gain Decreased bone mass Muscle cramps Acne Seborrhea Hirsutism
GnRH analogues	Downregulates GnRH receptors on pituitary Suppresses ovarian estrogen production Leads to amenorrhea and regression of endometrium and endometrial implants	Reduces pelvic pain	High rate of recurrence of symptoms after stopping Deterioration of lipid profile Depression Decreased libido Hot flashes Urogenital atrophy Decreased bone mass
Aromatase inhibitors Letrozole Anastrozole Exemestane	Reduces extra ovarian estrogen concentration Inhibits the aromatase conversion of steroidal precursors into estrogens Decreases expression of COX-2	Reduces abdominal-pelvic pain Treatment of recto-vaginal endometriosis	Headache Joint stiffness and joint pain Nausea Diarrhea Flushing Osteopenia/ osteoporosis
Selective estrogen receptor modulators	Estrogen-antagonistic activity at endometrial level	Current data in human studies do not support use	
Immunomodulators Pentoxifylline Infliximab Etanercept	Replaces platelet aggregation by inhibiting platelet phosphodiesterase Suppresses TNF-α, decreasing adhesion and growth of endometrial cells Suppresses angiogenesis IL-12: acts on T and NK cells to increase cytotoxic activity to limit endometrial implantation and growth	Not enough evidence to support use in the management of pain or infertility associated with endometriosis	Increased risk of infections, malignancies

(*continued*)

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Table 3 (continued)

Medication	Mechanism of action	Effects	Side effects
Melatonin	Scavenger of free radicals Broad spectrum antioxidant	No human data	
Selective progesterone receptor modulators Mifepristone Asoprisnil	Induces amenorrhea: mechanisms not yet fully understood	Improves pain Regression of endometrial implants	No significant report
Antiangiogenic agents	Blocks vascular endothelial growth factor Limits implantation and proliferation of endometrial implants	No human data	

Second-line treatment with GnRH analogues works by suppressing GnRH receptors of the pituitary, leading to hypoestrogenism that will subsequently lead to amenorrhea and atrophic regression of endometrial implants. Symptom reduction is seen in up to 50 % of patients, but use is limited due to the worsening of lipid profiles, depression, hot flashes, urogenital atrophy, decreased libido, and loss of bone density. These side effects can be combated with use of bisphosphonates and "add-back therapy" with HRT (hormone replacement therapy). GnRH antagonists recently have been studied, but more clinical trials are necessary before they can be introduced into clinical practice. The mechanism of action is reduction of estrogen levels, but with the advantage of not triggering side effects associated with estrogen deprivation [47].

Aromatase inhibitors, such as letrozole, anastrozole, and exemestane, act by decreasing the conversion of steroidal precursors into estrogen, which also stimulates the expression of COX-2. By blocking this pathway, growth of endometrial tissue is limited and inflammation caused by COX-2 is reduced. Side effects include headaches, nausea and diarrhea, flushing, joint pains and stiffness, and loss of bone density. The effect of these medications is reversible, and "add-back therapy" with HRT or bisphosphonates can be used to combat some of the side effects. Pelvic pain is reduced with use, but will recur after medication discontinuation [47].

Endometriosis is associated with increased free radicals and decreased antioxidants, and melatonin is both a scavenger of free radicals and a natural antioxidant. Use of melatonin has been studied in mice with endometriosis, and results have shown reduced endometrial lesions and increased antioxidant activity [47].

Angiogenesis is the process by which new blood vessels are formed and is necessary for endometrial implants to proliferate. The most important angiogenic factor in the pathogenesis of endometriosis is vascular endothelial growth factor (VEGF). Levels of VEGF are directly correlated to the severity of the disease. By blocking VEGF, the endometrial implants will be unable to proliferate or maintain established implantation. Animal models using antiangiogenic agents have favorable results; no studies have been conducted in humans [47].

Immunomodulators have also been looked at for treating pain and infertility associated with endometriosis, based on the increased levels of cytokines found in the peritoneal fluid of women with endometriosis. Pentoxifylline can suppress the action of TNF-α and vascular endothelial growth factor and influence endometrial implantation, but conflicting results have been obtained in the human studies. Infliximab and etanercept have also been studied in baboon models, again with limited data in humans.

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A Cochrane review has shown that there is not enough data to support the use of immunomodulators in the treatment of endometriosis associated pain or infertility [47].

Treatment of Endometriosis

See Table 3.

Female Infertility

Infertility is defined as the inability to conceive after 1 year of unprotected, regular intercourse or after 6 months if the female partner is aged 35 years or older [48, 49]. A survey from 2006 to 2010 found that over one million US women reported the inability to conceive, with over six million women reporting impaired ability to conceive or carry a pregnancy to term [49]. Similar to rates in other industrialized nations [49], nearly seven million individuals sought out infertility care [49]. Infertility can be due to the female component, the male component, or a combination. Female factors for infertility are discussed here and include ovulation disorders, uterine abnormalities, tubal obstruction or abnormalities, and peritoneal causes [49]. Further, the World Health Organization categorizes ovulatory disorders into three groups. Group I makes up 10 % and is characterized by hypothalamic-pituitary failure. Group II encompassing the majority, 85 %, includes polycystic ovarian failure and other disorders of dysfunction of the hypothalamic-pituitary axis and hyperprolactinemia. Group III, ovarian failure, is made up of approximately 5 % of ovarian disorders [49].

Initial history can assist in identifying a primary cause for infertility and help guide the initiation of the evaluation. Menstrual history, timing and frequency of coitus, prior use of contraception, prior pregnancies and outcomes, pelvic or abdominal infections, mediation use, occupational exposures, substance use, caffeine intake, alcohol and tobacco use, and prior surgery on abdominal and pelvic organs are all important components to a patient's infertility history upon presentation [49].

Ovulation Disorders

Ovulation is suggested in the presence of regular menstrual cycles, and infertile women with this history can be offered serum progesterone testing at day 21 from the first day of their last menstrual period to confirm [49]. In the setting of irregular menses, testing should be conducted later, starting 7 days prior to the onset of predicted onset of menses and continued weekly until it occurs [49]. Serum progesterone levels, drawn at day 21, of 5 ng per mL or higher suggest ovulation [49]. Levels less than 5 ng suggest anovulation, and further investigation should ensue to evaluate for thyroid disorders, hyperprolactinemia, and the like based on symptoms [49].

Serum FSH levels drawn at days 3–5 of the menstrual cycle can assist in determination of ovarian failure. A level of 30 mIU/mL or higher associated with a low estradiol level suggests ovarian failure, and a FSH of 10 mIU/mL or less with low estradiol levels suggests hypothalamic-pituitary failure [49].

Use of urinary LH kits can predict ovulation 14–48 h prior to ovulation and has largely replaced basal body temperature monitoring [48]. Postcoital testing is considered obsolete [48, 49].

Uterine Abnormalities

Structural uterine abnormalities, such as fibroids or bicornuate uterus, can be assessed with ultrasound or hysteroscopy [48, 49]. Fibroids invading the submucosa and intracavitary components of the uterus are associated with lower pregnancy implantation rates [51]. Müllerian abnormalities leading to a septate or bicornuate uterus are associated with the poorest reproductive outcomes [51]. Scarring of the endometrial lining, endometrial polyps, and synechiae are also associated with infertility [50]. Endometrial biopsy to

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determine endometrial dating has not been proven to be predictive of fertility outcomes and should be reserved in cases of suspected chronic endometritis or neoplasia [49].

Tubal Obstruction and Abnormalities

Tubal abnormalities from underlying disease processes or scarring from infection affect fertility by preventing the normal transport of the female oocyte through the fallopian tube. Tubal obstruction can be suggested if pelvic inflammatory disease or other pelvic infections are reported in the history. Most common organisms implicated in PID are gonorrhea and chlamydia, but tuberculosis infection has also been seen as a cause to tubal obstruction [52]. Additionally, endometriosis can cause tubal damage from inflammatory processes due to cytokines, damage to the fallopian tubes from abnormal endometrial implants, and production of adhesions [52]. Evaluation of tubal obstruction is best performed with hysterosalpingography because of its minimally invasive technique and potential therapeutic effect, but if concomitant pathology is suggested by history, a laparoscopy may be indicated [49].

Peritoneal Causes

Adhesions due to prior infections, surgeries, or endometriosis can also contribute to infertility by obstructing or altering the structural function of the fallopian tubes. Laparoscopy is indicated in the evaluation of suspected peritoneal pathology and can be used to lyse adhesions if felt to be contributing to the cause of infertility or, in some cases, pelvic pain [48, 49].

Treatment

The underlying pathology leading to ovulatory dysfunction, such as thyroid disorders, should be corrected when possible [48]. Hypothyroid patients can be corrected with levothyroxine, and hyperthyroid patients can be treated with methimazole, propylthiouracil (PTU), radioactive iodine (Graves' disease), or thyroidectomy. Hyperprolactinemia us treated with dopaminergic agents such as bromocriptine, which can restore ovulation [48]. In patients with PCOS, insulin-sensitizer metformin has been found to increase ovulation although it is not FDA approved for treatment of infertility [48]. Clomiphene citrate is an oral agent that can be used to induce ovulation. A dose of 50 mg a day, on days 3–5 of the menstrual cycle, for 5 days is administered. Ovulation can be determined by basal body temperature monitoring or urinary LH kits [48] or a serum progesterone [49]. If ovulation is not achieved, an increased dose of 100 mg for 5 days can be used. If a higher dose fails to induce ovulation, referral to a fertility specialist is recommended [48, 49]. Side effects of clomiphene citrate include hyperstimulation of the ovaries resulting in twinning or higher-order pregnancies, thrombosis, and increased risk of ovarian cancer [49].

Fallopian tube obstruction is often surgically managed, although success rates are reported as low, and risk for ectopic pregnancies is increased [48]. In vitro fertilization may be indicated if the tubes are markedly damaged [49]. Surgical correction has been successful in the case of submucosal fibroids through myomectomy and has been successful in treating infertility related to uterine abnormalities [50].

Unexplained Infertility

Upward of 30 % of infertility is unexplained [49]. Timing of intercourse with the use of urinary LH kits should be discussed. Also optimizing the health of both partners is key, with avoiding use of tobacco, caffeine, and illicit substances, limiting alcohol, and losing weight to obtain BMI of 30, to name a few of the lifestyle changes recommended [49]. Options for treatment may include use of clomiphene citrate with or without intrauterine insemination [48], but are unlikely to be successful [49]. In vitro fertilization has not been found of benefit in patients with unexplained infertility [48]. Because 50 % of couples who do not conceive in the first year do conceive in the second, couples should be counseled of such prior to engaging in invasive reproductive assistance. Due to the stress that infertility can cause in individuals, the

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couples should also be offered psychological counseling, noting that stress can also contribute to infertility [49].

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Family Medicine
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Disorders of the Neck and Back

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1 Disorders of the Back

1.1 Low Back Pain (LBP)

1.1.1 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].

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,

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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

"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 [11]. 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. The current model of episode onset and resolution is currently being challenged in favor of LBP as a chronic relapsing and remitting condition, with differing individual rates of relapse [12]. 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 first 12 months following a low back pain episode with a prior episode of LBP being the only strong predictor of future recurrence [13].

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.

1.1.2 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

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to established risk factors for back pain such as known trauma, previous low back pain, missed work, occupational mechanism, and preexisting mood disorder [14].

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 [15]. 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 [16]. 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 raising 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 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,

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)

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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 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.

These maneuvers may be most useful in those patients with symptoms suggestive of lumbar radiculopathy, such as radiating pain, numbness, or weakness. While the SST and the SLR exhibit similar rates of specificity (0.83 and 0.89), the SST is more sensitive (0.84 vs. 0.52) [17]. The cSLR and cFST are poorly sensitive but highly (>90 %) specific [18]. Thus, neural tension tests may be better applied to those with presenting symptoms 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) [18].

Further examination should include the hips and sacroiliac joints. Range of motion of the 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 [19].

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1.1.3 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 [20, 21]. 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 1806 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 [22]. 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 [21].

Plain-film radiography is best used as an initial evaluation when vertebral compression fracture is of utmost concern, such as those with osteoporosis or with chronic steroid use. Some authors have suggested the use of plain-film radiography combined with the erythrocyte sedimentation rate (ESR) as a cost effective means of addressing risk for cancer or inflammatory spondyloarthropathy. 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 [23].

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 severe 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. 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 [24].

1.1.4 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 injury that account for the most common types of low back pain [25].

Osteoarthritis Degenerative osteoarthritis of the axial spine is estimated to be present in 40–85 % of individuals [26], 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 [26].

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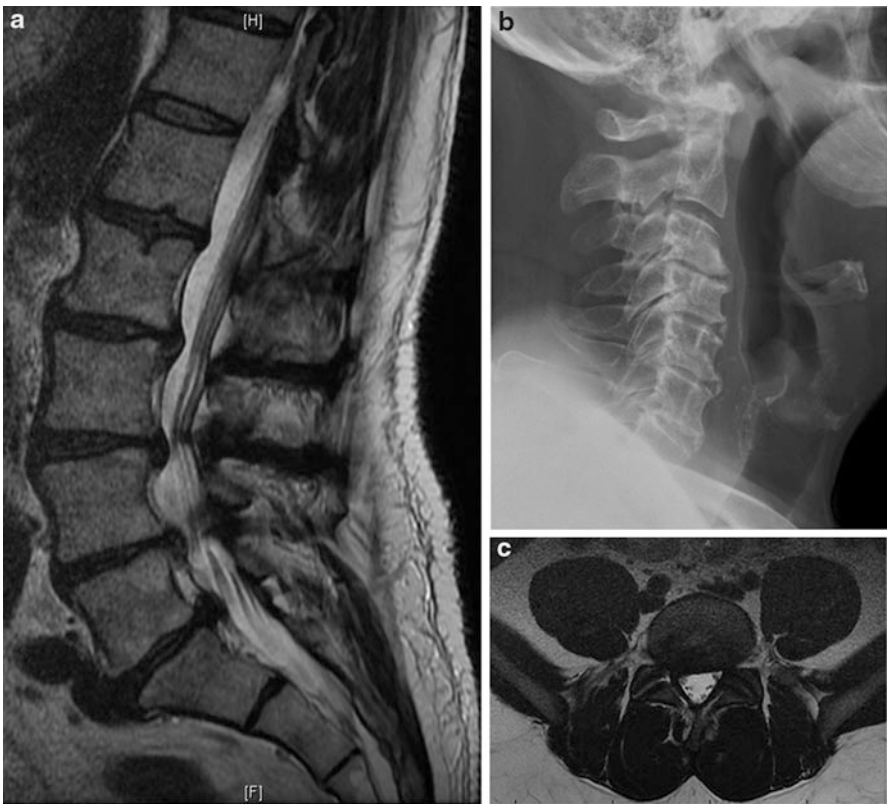

Fig. 1 Imaging of the pathologic spine. (**a**) T2-weighted sagittal MRI image of the lumbar spine of a 64-year-old man reveals multilevel spondylosis with disk pathology including protrusion and extrusion with migration at levels L3–L4, L4–L5, and L5–S1. (**b**) Plain-film x-ray image of lateral cervical 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

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 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 [27].

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 [27]. Paresthesias and numbness may be present and with prolonged symptoms weakness may occur in the distal musculature from lower motor neuron compromise.

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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 [28].

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 [29]. 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. 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.

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. There is insufficient evidence to recommend for or against pharmacological intervention or physical therapy (grade of recommendation, I), while the use of a lumbosacral corset is associated with increased pain-free walking distance. Epidural steroid injections may provide short-term (up to 6 months) relief in patients with radiculopathy or neurogenic claudication; these injections should be fluoroscopically guided. If medical/interventional treatment of moderate spinal stenosis is insufficient, surgical decompression is suggested to improve outcomes and patient pain scores [29].

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 [30]. 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 [16]. 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 [31].

Neoplasia Fewer than 1 % of individuals presenting to primary care offices with back pain will be diagnosed with a malignancy [16], and the spine is a more common site of metastasis than primary tumor. 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 ESR.

Symptomatic secondary metastases are estimated to occur in approximately 10 % of all cancer patients, and cadaveric studies find 30–90 % prevalence of spinal metastases [32]. Spinal metastases are most

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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 [33]. 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 [34]. 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 [34]. 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 [35], 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 [36].

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

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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 [36].

1.1.5 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 [37]. 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" [37]. 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 non-stratified control group. The low-risk group intervention was found to be non-inferior 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 [37].

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 [38].

Thus, stratified care for low back pain is shown to demonstrate moderate clinical and economic benefits and can be implemented successfully into a family medicine practice.

Activity For most patients, especially those with nonspecific low back pain, rapid return to normal activities, including work, is 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

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by inactivity. Joint stiffness and loss of capsular compliance begin soon after immobilization. The risk of thromboembolic event, pulmonary atelectasis, and pressure ulcers rise 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 [39]. Regular activity as tolerated maximizes the return to function and decreases patient pain score report.

Pharmacological

Non-opiate 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 first-line 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 [40]. 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 intra-family 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 [40].

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 [41]. Primary among these recommendations include time-limited rather than symptom-limited course of medication. Acute pain should be treated with short-acting opioids, while the use of long-acting slow release formulations may decrease euphoric effects and therefore abuse potential. Common adverse effects 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 [41]. 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.

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Skeletal Muscle Relaxants Medicines known as "skeletal muscle relaxants" are neither related 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 [40]. 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 [42]. 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 [40].

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, and desvenlafaxine carry for 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 [42].

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 [40].

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 [40]. There is, however, an established role for these medications for the treatment of diagnosed inflammatory spondyloarthropathies [43].

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 [44], 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 [45].

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 2005 study analyzed nineteen randomized controlled trials that study the effects of back schools on nonspecific low back pain. While only identifying six studies of rigorous methodology, it was concluded that there is moderate evidence indicating decreased pain and improved function or work status in an occupational setting over short and intermediate time frames when back schools were compared to pharmacological treatment, myofascial therapy, or placebo [46]. Thus, in certain applications, back schools may play an important role in the treatment of low back pain.

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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 [47].

Spinal Manipulation A 2004 Cochrane meta-analysis concluded that spinal manipulation was superior only to sham treatments and inert interventions. It demonstrated no advantage of "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 [48].

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 [49].

Surgery Evidence is very clear that there is no role for surgery of the spine outside the conditions of sciatica, pseudoclaudication, or spondylolisthesis [50]. 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 most common diskectomy approaches are standard and microscopic lumbar diskectomy (MLD), distinguished by the size of incision, amount of excised tissue, and use of magnification to improve precision. A 2012 meta-analysis comparing the two declared that the MLD approach was equivalent to the standard approach in terms of patient pain improvement and may present fewer complications due to operative techniques. Further application of MISS has resulted in tubular transmuscular (micro) diskectomy, in which a tubular retractor is placed through the paraspinal musculature. The lack of statistical discrimination among many approaches indicates that currently the skill and expertise of the performing surgeon likely have the greater determination on outcome when compared to the surgical approach [51].

The largest and longest-term comparison between nonsurgical and surgical approaches was published as the ten-year follow-up to the Maine lumbar spine study ($n = 400$) [50]. 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 [50].

1.2 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

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mechanically induced, and then maladaptive physical and cognitive compensations produce a mechanism for an ongoing pain [52].

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 level of fear avoidance and functional impairment predict recovery at 1 year time [53].

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 [54]. Therefore, many interventions attempting to prevent chronicity transformation have utilized psychological approaches. A 2013 study implementing CBT interventions to prevent chronicity transformation concluded that operant conditioning may be included in physical therapy practices toward this end [55].

2 Disorders of the Neck

2.1 Cervical Radiculopathy

2.1.1 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 was found to be 83 in 100,000 persons based on a recent study [56].

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.

2.1.2 Presentation

When compared to chronic spondylosis of the cervical spine, pain associated with radiculopathy is more commonly unilateral [57]. 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 occur in up to two thirds of patients, are more commonly associated with chronic spondylosis, usually characterized by facet joint osteophytosis or disk degeneration [27].

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 [57], 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.

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2.1.3 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 [56, 57]. 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 [58]. 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) [58].

2.1.4 Management

The prognosis of cervical radiculopathy is optimistic and well described [27, 56, 57]. 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. A 2011 evidence-based review addressed the available literature on the medical, interventional, and surgical management of degenerative cervical radiculopathy [58].

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 [58]. 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 % [58]. 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.

2.2 Acute Cervical Strain

2.2.1 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) [59]. 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 [59].

2.2.2 Presentation

Common symptoms after 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 [59]. 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

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the tort system, the median claim-closure time was 433 days and 57 % were still compensated at 1 year [60].

2.2.3 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.

2.2.4 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 [59]. 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 [59]. Patients should be educated and reassured regarding the positive prognosis [61]. Active therapy for comorbid mood disorders should be addressed immediately. Return-to-clinic and emergency room visit criteria should be discussed. If applicable, continuing care of mTBI should be provided [61].

2.2.5 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 [60]. The influence of jurisdiction on recovery is further highlighted by chronic whiplash, which is low in historically no-fault provinces (Quebec), less litigious countries (Greece), and where whiplash is not compensated (Lithuania) [60].

2.3 Cervical Myelopathy

2.3.1 General Principles

Chronic atraumatic compression of the cervical spine due to spondylosis is the most common cause of spinal cord compression in the world [62]. 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.

2.3.2 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 [63]. 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.

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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 [63].

2.3.3 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 [63], 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 [63].

2.3.4 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. Referral or comanagement with a neurologist is recommended. For individuals with moderate to severe or rapidly progressive myelopathic symptoms, surgical referral is warranted [64].

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Family Medicine
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Disorders of the Upper Extremity

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Because of the functional importance of the upper extremity to human activity, patients with injuries in this region frequently require diagnostic and therapeutic assistance from the family physician. A working knowledge of basic anatomy is helpful for establishing a differential diagnosis for upper extremity complaints. This chapter discusses common disorders in this region, but there are many unusual problems that may also present in an office situation.

1 Clavicle

The clavicle is the connecting strut that links the arm and shoulder with the axial skeleton. The clavicle is anchored medially by the sternoclavicular and costoclavicular ligaments, while the acromioclavicular and coracoclavicular ligaments anchor it to the scapula. A thorough examination of any shoulder injury should include palpation of the clavicle and evaluation of the acromioclavicular (AC) and the sternoclavicular (SC) joint motion.

1.1 Clavicular Fractures

Fractures of the clavicle, which account for 2–4 % of all fractures, have a bimodal distribution, with the most common causes from a direct blow to the shoulder or a fall on an outstretched arm. In young adults and children, mechanisms include sports injuries, motor vehicle accidents, and falls, while in the elderly, falls are a common mechanism [1]. The majority (60–80 %) of fractures occur in the middle third of the clavicle. Historically, nonoperative treatment was advocated for almost all middle clavicle fractures, even with severe displacement. In recent years, however, there has been a reconsideration of the role of operative intervention for both return to play and reduction of complications in part due to improved surgical technique [2]. Because of remodeling capabilities, almost all midshaft fractures in children and adolescents can be managed nonoperatively. Either a figure-of-8 brace or sling can be worn for comfort, usually for 2–4 weeks, with some data suggesting that a sling may be better tolerated [2]. In adults, the incidence of midshaft complications such as nonunion or neurovascular compromise is often reduced by surgical intervention. While an individualized approach is currently advocated, those with fracture displacement, shortening, or significant comminution, and those with tenting of the skin do best with surgical intervention. When there is minimal displacement, a sling or figure-of-8 brace remains an appropriate treatment; however, the patient should be advised that there may be a permanent bump at the site of callus formation. Fractures of the distal third (15–25 %) will require surgery if there is evidence of displacement, while nondisplaced fractures may be managed without surgery. At times, painful long-term arthritis of the acromioclavicular joint will necessitate surgical resection of the distal clavicle. Fractures of the medial head of the clavicle are rare (5 %) and are generally managed without surgery. However, it is vital that the patient be assessed for a posterior dislocation of the medial head, usually by CT scan. Such an injury can compress the great vessels or compromise the airway. Immediate elevation of the impacted segment and urgent cardiovascular or orthopedic consultation are recommended.

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1.2 Acromioclavicular (AC) Joint Dislocations

Dislocations of the AC joint result from a direct fall onto the anterior shoulder. Management of this condition is determined by the extent of the dislocation. Specific treatment for this problem is covered in Chapter ▶ Bites and Stings.

1.3 AC Joint Arthritis

Osteoarthritis of the AC joint is a common condition causing anterior and superior shoulder pain with the potential for significant disability. Causes include primary degeneration of the fibrocartilaginous meniscus, posttraumatic (prior AC joint injury), inflammatory, and septic arthritis. Weightlifters and throwers are also at risk for this problem [3]. On examination, the patient is point tender over the AC joint. Forward flexion of the arm to 90° followed by adduction of the arm across the body (the crossed body adduction stress test) compresses the joint and reproduces the pain [4]. Initial treatment includes rest, ice, nonsteroidal anti-inflammatory drugs (NSAIDs), and avoidance of aggravating activity. For refractory cases, a corticosteroid injection into the AC joint using an anterior and superior approach may provide some benefit [3]. For cases unresponsive to conservative management, resection of the distal clavicle can alleviate persistent pain.

2 Scapula

Isolated injuries of the scapula are rare, but occasionally, a direct blow over the involved area results in a fracture [5]. Because of the high impact involved, scapular fractures are frequently associated with other thoracic injuries such as rib fractures and pneumothorax. Treatment for fractures of the body of the scapula includes immobilization with a sling until subsidence of pain within 2–4 weeks, followed by progressive exercises. If the acromion or glenoid is fractured, orthopedic referral is necessary because of potential implications to shoulder mobility and function [5].

3 Shoulder

As the pivotal connection between the upper extremity and the axial skeleton, the shoulder is a frequent source of musculoskeletal problems. Its great range of motion is available only at some compromise to bony stability. Most shoulder stability is provided by periarticular soft tissues. A careful physical examination attempts to identify which components are contributing to a specific problem. Disorders extrinsic to the shoulder may also cause referred pain to this area. An evaluation of the cervical spine should be included for any problem presenting as shoulder pain.

Functionally, the shoulder is composed of four joints: sternoclavicular, acromioclavicular, glenohumeral, and scapulothoracic articulation. The major joint is the glenohumeral joint, in which the humeral head is three times larger than the glenoid socket. A fibrocartilaginous glenoid labrum provides depth to the socket and adds stability. During overhead motion of the arm, the humeral head is maintained in the socket by the four muscles of the rotator cuff. Originating from the scapula, these muscles maintain fixation of the humeral head and, based on their humeral insertion, assist in various arm motions. The supraspinatus assists in abduction and forward flexion, the infraspinatus and teres minor create external rotation, and the subscapularis causes internal rotation [6]. Also, vital for proper shoulder motion are the scapulothoracic muscles (rhomboid, trapezius, serratus anterior) and the deltoid.

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3.1 Traumatic Dislocation of the Shoulder

3.1.1 Anterior Dislocation

The major traumatic injury to the shoulder is the dislocation of the humerus from the glenohumeral joint. About 95 % are anterior dislocations caused by a fall on an outstretched hand or resisted force when the shoulder is abducted and externally rotated [7]. Examination reveals a squaring of the shoulder, loss of the roundness of the deltoid muscle, prominence of the acromial edge, and an anterior mass which is the humeral head. The arm is held in slight external rotation and abduction. Before reduction is attempted, a neurovascular exam should access damage to the axillary nerve with loss of sensation and diminished deltoid contraction. This injury, present in up to 30 % of dislocations, is usually a transient neuropraxia that requires several weeks for recovery.

If evaluation reveals no other abnormality, then immediate reduction is acceptable, even without prereduction radiographs, before muscle spasm sets in and makes manipulation more challenging [8]. A number of maneuvers have been described to relocate the shoulder. Initial attempts emphasize gentle longitudinal traction on the arm while passive abduction and external rotation is performed. If there has been a delay, then sedation may be required to effect muscle relaxation. With any maneuver, care must be taken to avoid excessive torquing of the humerus, which could lead to humeral fracture or brachial plexus injury.

After relocation and repeat neurovascular evaluation, the patient is placed in a sling for immobilization. A rehabilitation program is then instituted to strengthen the supportive musculature, restore motion, and prevent recurrent dislocation. Young patients, especially under age 20, are at increased risk for recurrence (75–90 %), and there is now evidence to suggest that surgical stabilization be considered as the initial treatment for young physically active patients [8]. Surgery is often recommended for those with recurrent dislocations. For those over age 50, the risk of recurrent dislocation is much less (10 %), but the increased risk of adhesive capsulitis and loss of shoulder motion requires that early shoulder mobility be emphasized. In this population, an exercise program should be initiated after only 1 week of immobilization. Elderly patients are also at greater risk for concomitant avulsion fracture of the greater tuberosity or tears of the rotator cuff.

3.1.2 Posterior Dislocation

Posterior dislocations comprise only 3 % of shoulder dislocations but are missed on initial radiographs as often as 60–80 % of the time [9]. They should be particularly suspected if there is a history of seizures, alcohol use, or electrical injury. On physical examination, the arm is held in internal rotation, rather than the external rotation of an anterior dislocation. Orthopedic consultation should be obtained if this injury is suspected.

3.2 Periarticular Shoulder Problems

Most shoulder problems involve the soft tissue periarticular shoulder structures rather than the glenohumeral joint. Because these supporting structures are vital to stability, a small injury to one component may cause significant problems in shoulder motion and function. Classification is made difficult by frequent overlap of symptoms, and the phrase subacromial impingement syndrome is an umbrella term [10] which includes the following subsets:

3.2.1 Rotator Cuff Injuries

Patients with rotator cuff injuries present either with abrupt onset of pain after a fall or sudden activity associated with the acute onset of pain or with a more insidious onset over weeks or months, often aggravated by repetitive overhead use, due to chronic degeneration or inflammation. Those with cuff injuries tend to have more pain with overhead activities that affect the lateral aspect of the deltoid. The

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pain is worse with movement and eases with rest, but recurs at night with fewer distractions to the pain [6]. Impingement of the cuff occurs chiefly in the supraspinatus as it courses underneath the acromion and coracoacromial ligament.

Full-thickness cuff tears due to chronic impingement are more common in middle-aged or elderly patients. The tenuous vascular supply of the supraspinatus as it inserts on the humerus is a likely etiology. Examination will demonstrate limited range of motion and a painful arc between 60° and 120° where the cuff comes into greatest contact with the overlying acromial arch. When the patient is unable to hold their arm in 90° of abduction, a significant tear has occurred. Chronicity is implied when there is atrophy of the supraspinatus or infraspinatus tendons. Each tendon of the rotator cuff can be isolated and tested [10]. While small or partial cuff tears can be managed with physical therapy, larger cuff tears warrant MRI and subsequent orthopedic opinion for potential surgery. With any rotator cuff injury, an extensive rehabilitation program of 3 to 6 months will be needed to regain full motion and strength.

3.2.2 Subacromial Bursitis

The subacromial bursa separates the deltoid muscle from the underlying rotator cuff. Irritation of underlying structures, as with impingement, may result in an inflammatory bursitis. Often there is a history of overuse or trauma, followed by the insidious onset of pain and limited active range of motion. A corticosteroid injection using a lateral or posterior approach can provide dramatic relief [6]. Calcific tendonitis, usually within the insertion of the supraspinatus insertion, may cause an acute inflammatory reaction of the overlying subacromial bursa. Roentgenograms demonstrate a calcific deposit superior and lateral to the humerus. Needle aspiration of the calcific mass along with lidocaine and corticosteroid injection can relieve the pain. Other treatment options include extracorporeal shock wave therapy and ultrasound guided needling or surgical excision of the calcific deposit [11].

3.2.3 Biceps Tendonitis and Rupture

The long head of the biceps tendon, which is palpable in the bicipital groove, may be irritated as it courses through the glenohumeral joint within the subacromial bursa and inferior to the supraspinatus tendon on its way to its attachment at the superior sulcus of the glenoid labrum. Pain may be isolated to the biceps tendon, but more often there is diffuse tenderness throughout the subacromial region. The short head of the biceps attaches to the coracoid process and is rarely involved in inflammatory problems of the shoulder. In most cases, rupture of the long head of the biceps tendon occurs as a result of advanced impingement in middle-aged or elderly patients. There is a sudden pop associated with lifting a heavy object with the elbow in flexion [12]. The patient experiences mild discomfort with ecchymosis in the upper arm and a palpable bulge of the biceps muscle mass. Because the short head of the biceps remains intact, treatment is usually symptomatic as little functional loss occurs. Surgery is generally reserved for high-performing athletes and manual laborers who need full supination strength and those who cosmetically object to the "Popeye" deformity that results from the tear. In contrast, rupture of the distal biceps tendon results in significant loss of 60 % of supination strength [13] and will often require surgical repair.

3.3 Glenohumeral Disorders

3.3.1 Osteoarthritis

Because it is non-weight bearing, the true glenohumeral joint is subject to less mechanical stress than the lower extremity. Arthritic changes often occur in response to prior injury. Inflammatory arthritis with erosive changes and joint effusions may occur with severe rheumatoid arthritis. Treatment for any degenerative arthritis is primarily aimed to relieve pain and inflammation, including rest, NSAIDs, physical therapy, and corticosteroid injection into the true joint space. Surgical intervention with joint replacement is an option for refractory cases [6].

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3.3.2 Labral Injuries

The fibrocartilaginous labrum serves to deepen the glenoid fossa and increase glenohumeral stability. Injuries to this structure can occur via several different mechanisms, including traumatic subluxation of the glenohumeral joint, and with excessive throwing. Advances in shoulder arthroscopy along with imaging such as MR arthrogram have improved assessment of these injures. The most common injury is a SLAP lesion, defined as superior labral anterior-posterior, and is best described in overhead athletes. While there may be some role for physical therapy, many injuries are best treated with arthroscopic repair, especially in young active athletes [14].

3.3.3 Adhesive Capsulitis

A poorly understood entity, adhesive capsulitis (also termed frozen shoulder or periarthritis) is characterized by a progressive, painful restriction of shoulder motion. Primary adhesive capsulitis has no apparent initiating event, is more common in the nondominant shoulder of women aged 40–60, and is bilateral in 20 % of cases [15]. When there is a secondary cause of shoulder stiffness such as immobilization, cuff injury, and trauma, the prognosis may not be as good, with permanent loss of shoulder motion. Initial treatment for either kind includes NSAIDs, corticosteroid joint injection, oral prednisone, and physical therapy. For refractory cases, surgical options include manipulation under anesthesia or shoulder arthroscopy [10].

3.3.4 Osteonecrosis

Although less common than osteonecrosis (avascular necrosis) of the femoral head, osteonecrosis of the humeral head can be caused by a number of illnesses such as alcoholism, sickle cell disease, and Gaucher's disease and as a consequence of proximal humeral head fractures [16]. The most common cause, however, is long-term steroid use. MRI may be useful for early diagnosis, as radiographs do not show subchondral collapse and humeral head flattening until later in the disorder. Treatment depends on the severity and chronicity and includes rest, analgesics, physical therapy, and arthroscopic debridement and core decompression for early cases. For more advanced disease, hemiarthroplasty or total joint arthroplasty may be the only options available.

4 Humerus

Proximal humeral fractures are common osteoporotic fractures which occur in elderly patients after a fall on an outstretched arm, with the fracture line occurring at the surgical neck of the humerus. While they are often impacted, fortunately about 76 % of these fractures are nondisplaced and can be managed nonoperatively (Fig. 1). Initial evaluation should include neurovascular assessment of the brachial plexus, axillary nerve, and axillary artery. If there is less than 1 cm displacement and less than 45° of angulation, treatment is by sling immobilization for 1–2 weeks followed by supervised active range of motion. The major complication is loss of joint mobility with potential development of adhesive capsulitis. Even with rehabilitation, some loss of shoulder abduction can be expected.

When a fracture involves the greater or lesser tuberosity or there is associated humeral head dislocation, there is greater risk of long-term complications including rotator cuff injury in up to 40 % of patients [16], and orthopedic consultation should be obtained. With trauma to the humeral shaft which occurs with young patients from high-velocity injuries, integrity of the radial nerve should be tested.

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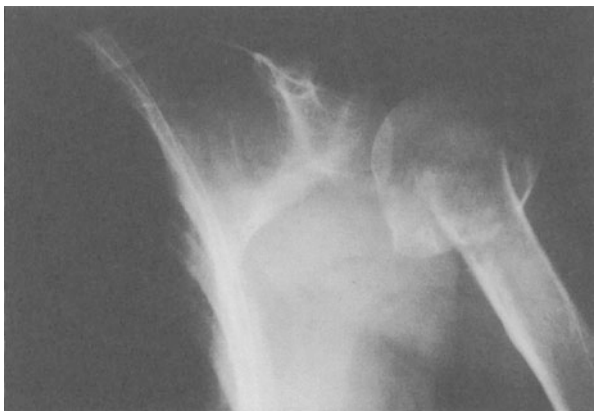

Fig. 1 This impacted humeral fracture in an elderly woman is neither displaced nor severely angulated. It was successfully managed with an arm sling for a week followed by rang-of-motion exercises and course of physical therapy (Originally published in Taylor [17], published with kind permission of Springer Science+Business Media New York, 2003. All rights reserved)

5 Elbow

5.1 Fractures of the Radial Head

While most elbow fractures are complex and require orthopedic referral, in adults the one third that involve the proximal radial head and neck can often be managed by the family physician. The patient presents with a history of a fall on an outstretched hand, pain on rotation or elbow extension, and tenderness over the radial head. Radiologic examination is important, as the fracture is often subtle. At times, the only finding is a posterior fat pad sign which occurs when blood that has entered the joint space displaces the fat pad posteriorly. A small anterior fat pad is a normal finding, but a large anterior fat pad, or "sail sign," is also indicative of a radial head fracture (Fig. 2). Criteria for orthopedic referral include >2 mm fracture displacement, >3 mm depression of the head, $>30^\circ$ fracture angulation, severe comminution, $>$ one third of the articular surface involved, and mechanical block to movement [18]. Management of a nondisplaced radial head or neck fracture emphasizes pain relief and early mobilization. A sling and posterior elbow splint extending from mid-humerus to beyond the wrist are worn for 1–2 weeks, and forearm rotation is begun as soon as pain permits, usually within a few days. Regular follow-up for this injury is important, as it may take several months for the patient to regain motion and some degree of extension, and 10–15° loss of full extension is common but does not affect function. With severe angulation of the radial head or severe fracture angulation, surgical repair may be necessary. In adults, excision of the radial head is one consideration, but in children, the radial head is necessary for adequate lengthening of the radius.

5.2 Epicondylitis

5.2.1 Lateral Epicondylitis

A common source of lateral elbow pain, lateral epicondylitis typically affects the dominant extremity and is usually associated with repetitive and forceful activity involving wrist extension. The eponym of "tennis elbow" is somewhat of a misnomer because the problem occurs more often in patients ages 30–64 and in nonathletic circumstances. The process is more degenerative from repetitive microtrauma rather than inflammatory and is generated by repetitive wrist extension especially by the proximal attachment of the extensor carpi radialis brevis (ECRB) into the lateral epicondyle. The condition is usually self-limited, although recovery may take 12–18 months for spontaneous resolution. A number of treatment options have been attempted including corticosteroid injection, ultrasound therapy, iontophoresis, botulinum

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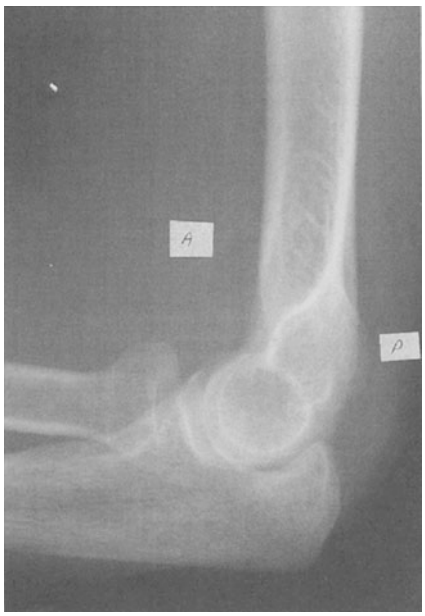

Fig. 2 Fat pad signs. A nondisplaced radial head fracture with both a posterior (P) and a prominent anterior (A) fat pad evident on this lateral view. The posterior fat pad is indicative of blood in the joint space from an occult fracture, displacing the fat from the joint space (Originally published in Taylor [17], published with kind permission of Springer Science+Business Media New York, 2003. All rights reserved)

toxin A injection, prolotherapy, low-level laser, platelet-rich protein injection (PRP), autologous blood injection (ABI), extracorporeal shock wave therapy (ESWT), bracing, and physical therapy. Current literature does not support any treatment as more effective for this disorder [19]. For the unusual situation where there are continued symptoms and disability in spite of other treatments, a number of surgical options both open and arthroscopic are available. For initial assessment, patients should at least be counseled to avoid the offending activity when possible, obtain ergonomic relief (such as adjusting a computer workstation), and use a "palms up" approach for lifting to use wrist flexors thereby resting the wrist extensors.

5.2.2 Medial Epicondylitis

Known by the eponym of "golfer's elbow," medial epicondylitis affects the musculotendinous origin of the common flexor component of the lower arm region where it attaches to the medial epicondyle. The clinical conditions are similar to those in patients with lateral epicondylitis, although this entity is less frequent in occurrence. The important difference is that pain occurs with activity of the flexor compartment of the wrist, and there is often palpable tenderness over the medial epicondyle. As with lateral epicondylitis, a number of treatment modalities have been attempted without any definitive preference.

5.3 Nursemaid's Elbow (Annular Ligament Displacement)

Previously described as subluxation of the radial head, nursemaid's elbow is now referred to by the more anatomically correct term annular ligament displacement. This injury typically occurs in a child ages 6 months to 5 years when there is traction force applied to a pronated arm, causing the annular ligament to slip over the radial head and become trapped in the radiohumeral joint. The patient will hold the arm in pronation and slight flexion against the body. Two forms of reduction have been described. Supination of the elbow with simultaneous flexion has a long history of success, but a more recent description of hyperpronation followed by extension may have a slightly better reduction rate [20]. If the history of

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injury is consistent and the manipulation is successful, no radiographs are necessary, as recovery by the child is almost immediate. To prevent recurrence, parents and caregivers should be educated about the injury mechanism for this benign entity.

5.4 Olecranon Bursitis

Due to its subcutaneous location, the olecranon bursa is susceptible to pressure, trauma, infection, and inflammatory conditions. Olecranon bursitis may be septic or aseptic in nature, although the clinical appearances of the two entities have overlapping features. The optimal management of this entity is ill defined. When infection is suspected, either antibiotics alone or aspiration with antibiotics is performed, with surgical drainage as an option for severe or refractory cases. The most common infecting organism is *Staphylococcus aureus*. With routine aseptic bursitis, or with traumatic bursitis, aspiration of joint fluid is often performed. For aseptic bursitis, the fluid is serous, sanguineous following trauma, and purulent in the case of infection or inflammation such as gout or rheumatoid arthritis. The use of corticosteroid injection may be attempted in recurrent aseptic bursitis, although there is little evidence for significant improvement [21]. When recurrent bursitis results in a thickened fibrotic mass, the only recourse may be surgical excision of the entire bursa.

6 Wrist

6.1 Fractures of the Distal Radius

Because of the close proximity to the radiocarpal joint, fractures of the distal radius are considered wrist injuries. In children, the most common injury is the buckle, or torus, fracture, which occurs with a fall onto an outstretched hand. Radiographic findings may be subtle, with only a slight cortical disruption of the extra-articular radius seen on a lateral film (Fig. 3). While a short arm cast for 3–4 weeks is an acceptable treatment, more recent data suggests that a splint for the same time frame is an acceptable treatment and potentially more cost-effective [22]. When a child presents with a "sprained wrist," evaluation must be done carefully, as the epiphyseal plate is weaker than the ligaments during this period of rapid growth. With normal roentgenograms and tenderness over the epiphyseal plate, a Salter I fracture is presumed, with recommended immobilization for 2–3 weeks.

In adults, the most common radial fracture is Colles' fracture which occurs when a patient over 50 falls onto an outstretched arm. The "silver fork" deformity is caused by dorsal displacement of the distal fragment. The ulnar styloid may also be fractured. Reduction of Colles' fracture may be attempted, but the physician must be aware of potential complications of this fracture, including median or ulnar nerve compression, damage to the flexor or extensor tendons, and radioulnar arthritis [8].

Nondisplaced distal radial fractures that are nonarticular can usually be treated with cast immobilization for 6 weeks in adults. Low-impact intra-articular nondisplaced fractures in the elderly may only require cast immobilization, although the patient should be advised that some residual arthritis may occur. For displaced fractures or intra-articular fractures in young patients, treatments such as percutaneous pinning or open reduction with internal fixation may be required to minimize long-term problems in the joint [23].

6.2 Carpal Fractures

Approximately 60–70 % of carpal bone fractures involve the scaphoid, with young adults having the highest fracture incidence. The usual mechanism is a fall on an outstretched, pronated, and ulnarly deviated hand with the wrist in more than 90° of dorsiflexion. Fracture location and appearance determine the likelihood of complications, with proximal scaphoid fractures (15 %) having a higher risk of

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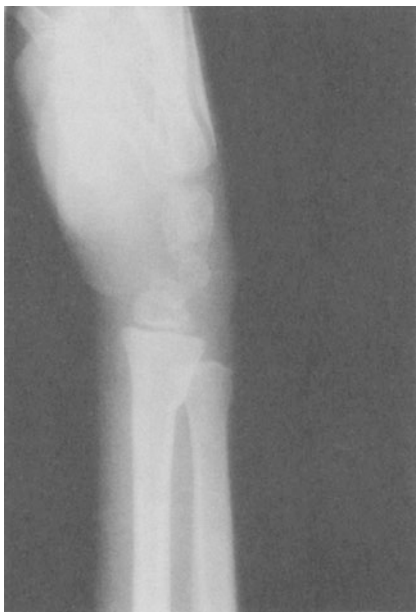

Fig. 3 Buckle (torus) fracture. A small cortical disruption is visible in the metaphysis of the distal radius (Originally published in Taylor [17], published with kind permission of Springer Science+Business Media New York, 2003. All rights reserved)

complications. Distal (5 %) and waist (80 %) fractures have a better prognosis than proximal (15 %) fractures, and if the fracture is nondisplaced, it can be managed by the family physician, although surgical intervention is an option when rapid return to sport or work is desired. A fracture more than 1 mm displacement, or any fracture with a delayed diagnosis, will also likely require orthopedic intervention [24]. Initial plain film radiographs may appear normal with undisplaced scaphoid fractures. When there is tenderness in the anatomic snuffbox (between the extensor pollicis brevis and extensor pollicis longus tendons) or the scaphoid tubercle (palmar hand surface), options include splint immobilization for 7–10 days with repeat radiographs or MRI. Because of the high risk of nonunion, scaphoid fractures require prolonged immobilization – generally 8–12 weeks for waist fractures. Because of the subtle nature of these fractures, often with little wrist swelling, there is a tendency by some patients to avoid initial treatment. Subsequent nonunion places the entire wrist at risk for significant avascular necrosis or arthritis, with more complicated and less successful salvage therapy performed to maintain vascular integrity and wrist congruence [24].

Other fractures of the carpal bones are uncommon and frequently require special radiographs or CT/MRI in order to visualize the pathology. The triquetrum is the second most commonly injured carpal bone (15 %), and if there is a nondisplaced fracture of the triquetrum, it can be managed by cast immobilization for 4–6 weeks [25]. A meticulous examination of the painful area indicates which carpal bones are likely to be involved. Because serious sequelae are common, including ulnar or median neuropathy and chronic wrist instability, orthopedic intervention is usually advised.

6.3 Wrist Instability

Although fractures of the carpal bones are unusual, sprains and other minor traumatic wrist injuries are common. A number of serious wrist injuries have been described as physicians have gained greater appreciation for the complex interactions of other ligaments and multiple articulations within the carpal complex [26]. The MRI has been especially useful in delineating wrist abnormalities, while plain radiographs may be helpful for certain problems such as lunate dislocations and scapholunate dissociations. Because distinguishing between a serious wrist injury and a minor sprain can at times be

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challenging, the physician should be suspicious about wrist injuries which fail to resolve within a 3–4-week period of time and proceed with MRI and/or orthopedic consultation.

6.4 TFCC Injuries

The triangular fibrocartilage complex (TFCC) is a small meniscus located distal to the ulna. This tissue serves to absorb impact to forces on the ulnar aspect of the wrist. Injuries can be acute, due to sudden impact, or chronic, due to repetitive loading such as gymnastics. As with carpal stability, the physician should be suspicious of TFCC injuries when ulnar wrist pain does not respond to 3–4 weeks of splinting. MRI findings will guide management which may include arthroscopic repair or debridement [27].

6.5 De Quervain's Tenosynovitis

A stenosing tenosynovitis, de Quervain's tenosynovitis occurs as the first extensor compartment, comprising the abductor pollicis longus and the extensor pollicis brevis tendons, courses over the radial styloid and through a fibro-osseous tunnel that holds the tendon against the bone. Thickness and swelling within this region produces radial-sided wrist pain associated with thumb movement. There is often an occupational or vocational history of repetitive hand motion such as knitting, sewing, or painting. The diagnosis is confirmed by the Finkelstein test and performed as follows: after passive adduction of the thumb into the palm, ulnar deviation of the wrist elicits a sharp pain that reproduces the patient's symptoms. Initial treatment will often include a corticosteroid injection, which has been shown to be successful 60–90 % of the time [28]. Other treatment options include NSAIDs and a thumb spica splint. On occasion, surgical release of the tendon sheath is required for symptomatic relief.

6.6 Intersection Syndrome

Inflammation can also occur at the crossover of the first and second extensor compartments of the wrist, located 4–8 cm proximal to the distal radius. Pain and tenderness are noted in this region, and at times there is fusiform swelling [29]. The problem occurs as an overuse syndrome from repetitive wrist extension, such as rowing, pulling, or weight lifting, and should be distinguished clinically from the more distal problem of de Quervain's tenosynovitis. Initial treatment should include splinting, relative rest, and NSAIDs, with corticosteroid injection reserved for more refractory cases.

6.7 Ganglion Cysts

Ganglion cysts are fluid-filled masses stemming from the joints of the hand or wrist, which can arise from many articulations. The most common locations are the volar wrist adjacent to the radial artery and the dorsal radial wrist adjacent to the scapholunate interval. Degeneration of the joint capsule leads to an extravasation of fluid through a 1-way valve. These lesions may be asymptomatic or painful with activity. Reassurance for asymptomatic lesions is appropriate; spontaneous resolution can occur in up to 42 % of patients over 6 years [28]. For symptomatic cysts, aspiration can be attempted although caution must be used with aspiration of volar cysts due to the close proximity to the radial artery. A large bore needle (18 or 20 gauge) is inserted into the mass and fluid, usually a thick jellylike substance, can be aspirated. There is a 30–40 % chance of resolution with aspiration. For recurrent ganglia, surgical excision can be offered, although even here there is a variable recurrence rate of as much as 40 % [28].

6.8 Carpal Tunnel Syndrome

The most common compressive neuropathy of the upper extremity, carpal tunnel syndrome, is discussed in Chapter ▶ Care of the Dying Patient.

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7 Hand

7.1 Metacarpal Fractures

The most common fracture is a "boxer's fracture," which is a fracture at the neck of the little finger that gets its name due to a high prevalence among amateur pugilists. Because of the mobility of the fourth and fifth metacarpals, volar angulation of the distal fragment of less than 30–40 is acceptable without the need for bone manipulation [30]. While angulation is acceptable, a rotation injury around the longitudinal axis of any metacarpal necessitates orthopedic referral for surgical pinning. For a boxer's fracture with mild angulation, an ulnar gutter or volar splint with the metacarpophalangeal (MCP) joint at 90° is applied for 3–6 weeks. Midshaft fractures of the fifth metacarpal can be managed similarly if the angulation is less than 20°. Nondisplaced fractures of the second and third metacarpals can be treated with a short arm cast, but careful physical examination must be performed to ensure that there is no rotation or angulation present, as these bone problems necessitate surgical correction. The unusual fracture that involves either the articular surface of the metacarpal base or metacarpal head mandates orthopedic consultation because of the potential for later complications.

Intra-articular fractures of the thumb require surgical correction, such as Bennett's fracture (with proximal dislocation of the metacarpal bone) or Rolando's fracture (a comminuted intra-articular fracture of the metacarpal base). The more common extra-articular fracture of the thumb, if not angulated more than 30°, can be managed with a short arm thumb spica cast with the thumb in a flexed position.

7.2 Arthritis of the Thumb

Arthritis of the basal joint of the thumb, the first carpometacarpal joint, is the second most common hand arthritis after DIP (distal interphalangeal) joint arthritis. Patients, often middle-aged or elderly females, complain of pain at the base of the thumb with vigorous activity. Progression of disease can lead to significant functional disability with simple tasks such as opening jars or turning doorknobs. Over time the base of the thumb enlarges, producing a "squaring of the thumb" on physical examination. A grind test, with axial loading of the CMC joint, will reproduce the pain. Radiographs will demonstrate narrowing of the joint space and osteophyte formation. Treatment options include activity modification, thumb splinting, NSAIDs, and intra-articular corticosteroid injections [28].

7.3 Infections

Prompt diagnosis and treatment are important with hand infections because hand stiffness, contractures, and even amputation can result from missed diagnoses or delayed treatment. *Staphylococcus aureus* remains the most common species with an increasing prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA). Immunocompromised patients (diabetes, HIV, IV drug users) are at higher risk and often will have polymicrobial infections [31].

7.3.1 Palmar Space Infections

Infections of the palmar space are potential disasters because spread in the deep space tissues can occur rapidly. Pain, tenderness, or swelling of the palmar surface suggests a deep hand infection, as does a recent history of minor trauma. Evidence of a palmar space infection mandates early orthopedic consultation, as surgical drainage is the primary intervention. Animal bites in this area will often warrant prophylactic antibiotics, especially the deep puncture wounds inflicted by cat bites [32].

7.3.2 Dorsal Hand Infections

Infections of the dorsal hand may appear worse than palmar infections because of the dramatic swelling within the loose connective tissue, but the prognosis is generally good. Oral antibiotics and outpatient

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drainage are usually satisfactory. Before treatment, however, the palmar surface must be inspected to be sure that the dorsal infection is not originating from a deep palmar infection that has ruptured to the dorsal surface. Lacerations over the MCP joints warrant special precautions, especially those of the fourth or fifth metacarpal. The usual history for this injury is an altercation in which the patient has punched another person in the teeth and sustained a human bite (fight bite). The patient frequently denies this history on initial questioning. A human tooth contacting a clenched fist usually violates the extensor tendon and joint capsule and may injure the metacarpal head, inoculating the MCP joint [32]. When this injury is suspected, a hand surgeon should be contacted to consider early operative debridement. A good rule to remember is that *all* lacerations over the MCP joints are human bites until proven otherwise.

7.4 Dupuytren's Contracture

Dupuytren's contracture is an idiopathic thickening of the palmar fascia, resulting in asymptomatic contractures of the fingers primarily at the MCP joint but at times involving the PIP joint. The subsequent deformity can be functionally disabling. Although the etiology is unknown, there is autosomal dominance with variable penetrance which occurs primarily in middle-aged men of Celtic origin [33]. The inflammation and subsequent contracture of the palmar aponeurosis may progress over many years. Treatment of this entity has been limited, and corticosteroid injections have not been beneficial. While surgical correction remains the mainstay of treatment, in recent years, the use of collagenase and other enzymatic injections has offered some promise as an alternative to surgery [33].

8 Finger

8.1 Fractures

8.1.1 Distal Tip Fractures

Crush injuries of the tip of the finger cause pain because of the closed space swelling. Even when the fracture is comminuted, the fibrous septae provide stability during bone healing. Protective splinting of the tip and DIP joint for 2–4 weeks should be followed by range of motion and strengthening of the DIP joint. Patients should be informed that these fractures are often complicated by hyperesthesia, cold sensitivity, pain, and numbness that may last for 6 months after the injury [34]. For any fracture associated with a nail bed injury, the nail bed or matrix must be repaired to minimize aberrant nail growth. Subungual hematomas, with or without associated fracture, can be decompressed with an electrocautery device or heated paper clip, creating a hole at the distal tip of the lunula.

8.1.2 Middle and Proximal Phalangeal Fractures

Examination to determine stability after a finger fracture is the key to management of these injuries. Assessment of angulation is made with radiographs, while rotation stability is determined by clinical examination. With finger flexion, all fingers should point toward the palmar thenar eminence [35]. Evidence of finger overlap indicates rotation instability, even if radiographs demonstrate minimal angulation (Fig. 4). Nondisplaced extra-articular fractures of the middle or proximal phalanx can be managed by 1–2 weeks of immobilization followed by dynamic splinting with "buddy taping" to an adjacent finger for 4–6 weeks during activity [35]. Large intra-articular fractures involving the middle or proximal phalanx are usually unstable fractures that will require percutaneous pinning or compression screws. Small (<25 %) avulsion fractures of the volar middle phalanx are frequent injuries that occur with a hyperextension injury (Fig. 5). In addition to the fracture, there is disruption of the volar plate, a structure that prevents hyperextension of the proximal interphalangeal (PIP) joint. These injuries are managed by 2–3 weeks of immobilization with 20–30° of flexion at the PIP joint, which allows maximal length of the collateral

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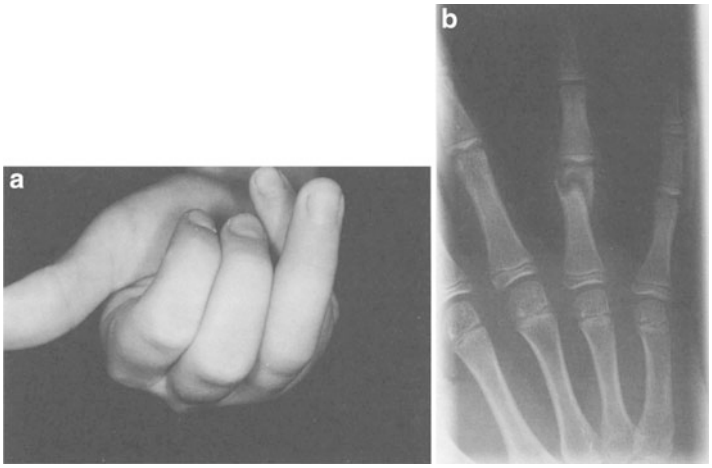

Fig. 4 Rotation deformity of the ring finger (**a**) indicates that surgical fixation is necessary to reduce the fracture. The radiograph (**b**), with only mild angulation, demonstrates why clinical examination for rotation is necessary for evaluating a finger injury (Originally published in Taylor [17], published with kind permission of Springer Science+Business Media New York, 2003. All rights reserved)

PIP ligaments and permits early finger rehabilitation. A buddy taping program during activity or sports, with gauze placed between the fingers to reduce skin maceration, should continue for an additional 4–6 weeks. Failure of the volar plate to heal properly may result in hypermobility at the PIP joint.

8.2 PIP Joint Dislocations

With sudden hyperextension, the middle phalanx may dislocate dorsal to the proximal phalanx. This dislocation, known as a "coach's finger," is easily reduced by gentle traction on the finger, with volar pressure on the middle phalanx of the PIP. Successful relocation produces immediate relief and resolution of the deformity [34]. Radiography should still be performed to look for evidence of subluxation, PIP joint instability, and middle phalanx volar plate fracture. Because the dislocation results in disruption of at least the fibrocartilaginous volar plate, the PIP joint should be immobilized in 20–30° of flexion and managed similarly to the volar plate fracture described above. Early range of motion exercises after just 1–2 weeks of immobilization have been shown to improve finger mobility and earlier return to function [34]. Lateral joint injuries with mild instability on stress testing (<15° of deviation) can also be managed with flexion splinting and subsequent buddy taping. Treatment of complete lateral dislocations and volar dislocations is more complex and referral to a hand surgeon is usually advisable.

8.3 Tendon Injuries

8.3.1 Mallet Finger Injuries

Forced flexion of the distal interphalangeal (DIP) joint on an extended finger avulses the extensor tendon as it inserts into the distal phalanx, and the patient cannot actively extend the distal phalanx. If left untreated, mallet finger leads to a swan neck deformity from PIP joint hyperextension and DIP joint flexion [36]. Orthopedic referral is indicated only if there is subluxation of the DIP joint or if there is a large bone fragment involving >25 % of the articular surface. Usually, radiographs will demonstrate either no fracture or only a small avulsion fragment. This injury is treated by placing the DIP joint in extension for a period of 8 weeks, while the PIP joint is permitted to move freely. A number of commercial and homemade splints are available, and there is no clear preferred method. The key is constant prolonged splinting, which is vital to permit tendon healing [36]. The patient is advised that flexion of the DIP joint even once before adequate healing will result in tendon avulsion and necessitate reinitiation of the entire

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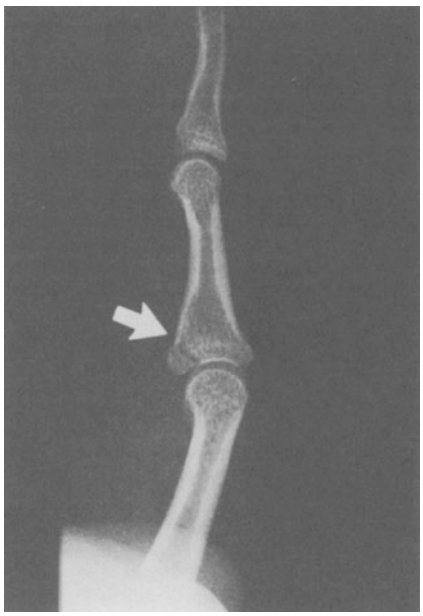

Fig. 5 This fracture of the middle phalanx implies that the distal volar plate has been disrupted. A combination of splinting and buddy taping for several weeks is required to allow the volar plate to heal (Originally published in Taylor [17], published with kind permission of Springer Science+Business Media New York, 2003. All rights reserved)

process. During any splint change, care is exercised to maintain finger extension. Hyperextension of the joint is also avoided, as this may lead to necrosis of the dorsal skin.

8.3.2 Central Slip Injuries

The central extensor tendon of the finger courses over the proximal phalanx and inserts into the base of the middle phalanx. A laceration or crush of the extensor tendon over the dorsum of the PIP joint, or volar dislocation of the PIP joint, damages the central portion of the extensor tendon. When this central slip is damaged, sudden forced flexion of the PIP joint results in loss of extension at the PIP joint and hyperextension of the DIP joint. The resulting contracture is known as a boutonniere deformity, named after the French term for buttonhole [37]. Tenderness of the central slip region is an injury to this structure until proven otherwise. A potential central slip injury without fracture is treated by maintaining the PIP joint in extension for 2–6 weeks. The stiffness that results from the collateral ligament tightening is much easier to treat than is correction of an established boutonniere deformity.

8.4 Trigger Finger

As the flexor tendon courses through the hand, a nodular thickening at the MCP level impinges the tendon. The cause is inflammation at the A1 pulley, the first of five pulleys which guide the flexor tendon into the finger. Although the problem is located at the MCP head, the patient will often complain of more distal pain at the PIP level. During finger extension, there is a catching or locking of the PIP joint as the stenosed tendon becomes trapped in the pulley. Trigger finger is more common in middle-aged women, in the dominant hand, and in patients with diabetes. Initial management is a tendon sheath injection with a small amount of a corticosteroid (e.g. 10 mg triamcinolone) directly into the stenosed area (Fig. 6). Initial steroid injection has a success rate of about 57 %; a second injection may increase the success rate to 86 % [38]. If the trigger finger persists, surgical release is necessary. For pediatric cases, a trigger thumb is more common than a trigger finger, and surgical intervention, not corticosteroid injection, is the recommended treatment.

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8.5 Gamekeeper's Thumb

Damage to the ulnar collateral ligament (UCL) that occurs with a sudden hyperabduction is termed a gamekeeper's or skier's thumb. The UCL is vital for open grasp and pinch action of the hand. Swelling and tenderness of the ulnar side of the MCP joint suggest this injury. A radiograph of the thumb is obtained to ensure there is no fracture before the UCL is tested. To examine for instability, the MCP joint is stressed with the interphalangeal (IP) joint in both extension and flexion to test both the accessory and proper components of the collateral ligament [39]. An unstable joint, which opens up >35° or 15° more than the normal contralateral UCL, or a radiograph which shows a large avulsion fragment, necessitates orthopedic referral for probable surgery. With a complete tear, the interposition of an adductor aponeurosis between the ends of the torn ligament (termed a Stener lesion) prevents ligament healing unless surgery is performed. Early repair within several weeks optimizes return of hand function. If there is tenderness, but the UCL is stable, a thumb spica splint or cast is applied for 1–2 weeks and the joint is then reassessed for instability.

8.6 Infections

8.6.1 Paronychia

Inflammation of the tissue immediately surrounding the nail, known as a paronychia, is commonly caused by an acute (<6 weeks) or chronic (>6 weeks) infection. The infection is often introduced by minor trauma such as nail biting (onychophagia) or manicuring. Redness and swelling occur along the nail folds and fluctuance is common. Early infections may be treated with warm soaks and topical or oral antibiotics [40]. Treatment of a superficial abscess involves a scalpel incision between the nail fold and the nail plate with evacuation of pus; a finger block before incision is optional. The incision is made parallel to the nail plate to avoid damage to the germinal nail matrix. In the unusual event of a deeper subungual abscess, more extensive surgery with partial nail removal is required to drain the abscess. A chronic paronychia is often associated with occupational water exposure such as dishwashing or bartending. The infecting organism is often *Candida albicans*. Environmental modification plus oral antifungal medication is often successful. Surgical management is reserved for refractory cases [40].

8.6.2 Felon

Painful abscesses within the distal pulp space, felons typically occur after a minor puncture wound. Tense distension within this closed space can cause compromise to soft tissues and digital vascularity [31]. Early surgical drainage is usually required to prevent loss of the pulp tissue or to prevent other complications such as osteomyelitis or tenosynovitis. Following a digital block, a felon is drained by one of several

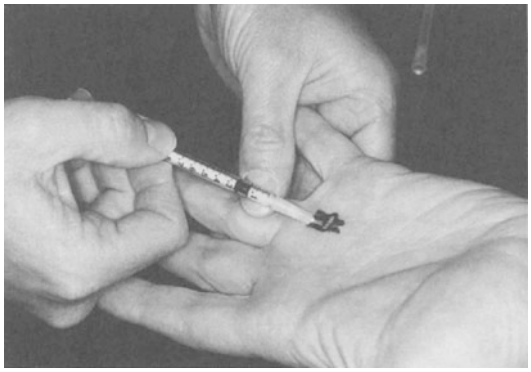

Fig. 6 Injection of a trigger finger is performed in the A_1 pulley at the MCP level. The needle can be directed proximally (as shown) or distally (Originally published in Taylor [17], published with kind permission of Springer Science+Business Media New York, 2003. All rights reserved)

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surgical techniques. A lateral incision or longitudinal palmar incision is most common. Incision of the radial side of the index and ulnar side of the thumb and little finger is avoided to prevent sensory problems in these sensitive areas. Packing material is placed and changed frequently along with administration of oral antistaphylococcal antibiotics.

8.6.3 Tenosynovitis

Pyogenic flexor tenosynovitis results when a puncture wound inoculates the flexor sheath. Kanavel's 4 signs of flexor tendonitis include a flexed resting posture of the digit, palpable tenderness of the flexor sheath, fusiform swelling of the digit, and severe pain on passive extension [31]. The latter sign is the most specific for flexor tenosynovitis and mandates immediate surgical consultation, since early debridement and aggressive care may allow salvage of finger and hand function.

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Family Medicine
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Disorders of the Lower Extremity

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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

Hip fractures are extremely common. In 2010, there were 258,000 hospital discharges in the United States for hip fractures in those >65 and the rate increased 10 times for those >85. Thirty percent patients die within a year of their hip fracture [1]. 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, the prevalence is only expected to increase.

Diagnosis

Classically, patients will complain of a sudden onset of hip pain and inability to walk after a fall, although those with minimal displacement or impaction may be able to ambulate. Insufficiency fractures (normal stress to abnormal bone causing a fracture) may occur in the absence of overt trauma. Patients may also complain of groin, thigh, buttock, or knee pain. 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 (i.e., 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

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Table 1 Hip differential diagnosis 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

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 [1]. Thromboembolic events are potential life-threatening complications associated with hip fractures. Antithrombotic prophylaxis should be started with low-molecular-weight heparin 12 h after hip fracture surgery and continued for 14 days along with intermittent pneumatic compression until the patient is ambulatory [2].

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

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Table 2 Intrinsic and extrinsic risk factors for stress fractures and overuse injuries of the lower extremity

<table>
<tr><td colspan="2">Intrinsic risk factors</td><td colspan="2">Extrinsic risk factors</td></tr>
<tr><td>Hormonal factors
Leg length abnormality
Foot abnormality</td><td>(e.g., Estrogen deficiency)
Functional* vs. true**
Pes cavus/planus
Rearfoot varus
Hypermobile first ray
Short first ray or long second ray</td><td rowspan="3">Training regimen*</td><td rowspan="3">Volume
Intensity
Duration
Inadequate recovery time
New activity
Poor technique</td></tr>
<tr><td>Hip</td><td>Excessive hip external rotation
Femoral ante/retroversion</td></tr>
<tr><td>Knee</td><td>Genu valgum/varum
Patella alta
Tibia vara/torsion</td></tr>
<tr><td colspan="2" rowspan="2">↓ Muscle endurance
↓ Bone mass
↓ Lower body muscle mass</td><td colspan="2">Medications</td></tr>
<tr><td>Improper nutritional habits</td><td>♀ Athlete triad</td></tr>
<tr><td colspan="2" rowspan="2">Muscle imbalance
Genetic factors
Metabolic factors</td><td>Running surface</td><td>Hard
Soft
Canted</td></tr>
<tr><td colspan="2">Smoking</td></tr>
<tr><td colspan="2" rowspan="2"></td><td>Environmental factors</td><td>Hot
Cold
Humid</td></tr>
<tr><td>Improper equipment</td><td>Shoe**</td></tr>
<tr><td colspan="2">*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)</td><td colspan="2">*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)</td></tr>
</table>

strengthening is advocated [3]. 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 [1]. 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.

Stress Fractures

The lower extremities are the site for 80–95 % of stress fractures [4]. Table 2 lists intrinsic and extrinsic risk factors which must be addressed for prevention as well as recurrence avoidance. 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

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Table 3 Low- and high-risk stress fractures disorders 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
	Fifth metatarsal
	Treatment recommendations
	Refer to musculoskeletal specialist due to high morbidity
Correct risk factors	**Correct risk factors**

Consider bone mineral density testing if history of multiple low-risk stress fractures or a single high-risk stress fracture

(MRI) is the modality of choice for diagnosis. Stress fractures can be segregated into low and high risk depending on their ability to heal. See Table 3 for a list of each type of fracture and treatment recommendations based on type.

Around the hip, femoral neck stress fractures (FNS) require discussion as there is high morbidity if not promptly diagnosed and appropriately managed. Female athletes and those unaccustomed to running or impact forces (i.e., basic military recruit) are the most common patient populations. Pain can be focal or diffuse and even radiate to the knee. There is a paucity of physical exam findings. A high index of suspicion is required and radiographic assessment is mandatory if the diagnosis is considered. It would be prudent to have patients be non-weight bearing while awaiting a definitive diagnosis. If confirmed, all patients with FNS should be referred for definitive management [5].

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. Unless an avulsed fragment is displaced >2 cm, nonoperative management is recommended and consists of decreased activity with gradual resumption 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 [6].

Posterior dislocations are most common and present as a flexed, adducted, and internally rotated leg. Anterior dislocations are rare, more likely to occur during sporting events, and present 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®

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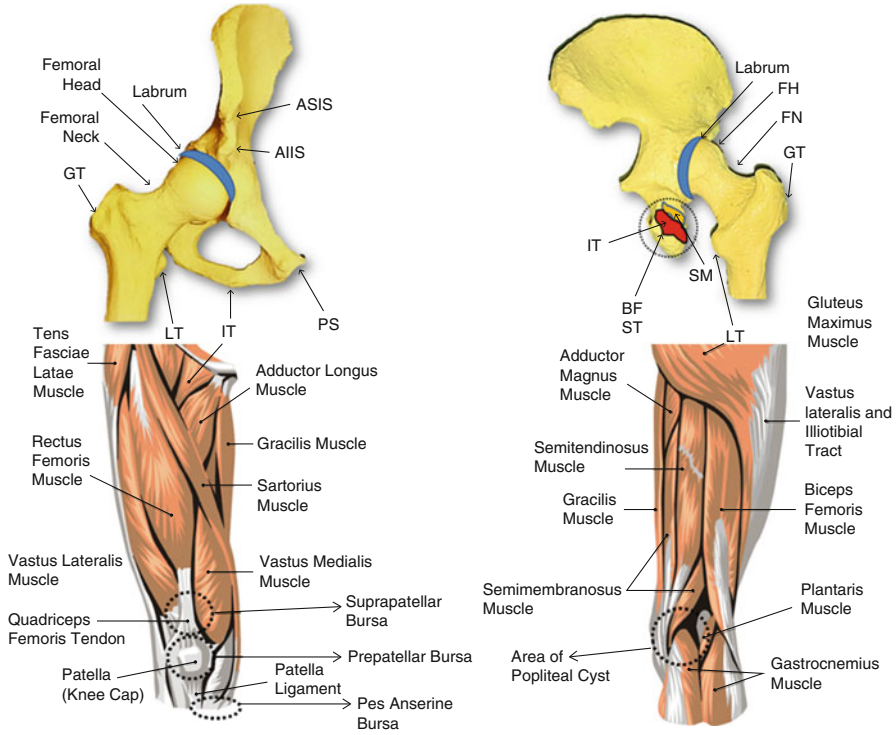

Fig. 1 Hip and upper leg anatomy. AIIS = anterior inferior iliac spine (rectus femoris origin); ASIS = anterior superior iliac spine (sartorius origin); PS = pubic symphysis (adductor brevis/longus and gracilis origin); IT = ischial tuberosity (hamstring origin (BF = biceps femoris/ ST = semitendinosus/ SM = semimembranous)); 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)

protocols and assessing 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-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 [6]. 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.

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Femoroacetabular Impingement (FAI)

General Principles

FAI comprises a constellation of bony overgrowth conditions in and around the hip joint. The condition is caused by supraphysiologic or excessive motion in normal hips or normal motion through the hips with atypical morphology which leads to bony changes and eventual impingement [7]. 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). General population prevalence is unknown as descriptive epidemiology has only been done at referral centers involving patients undergoing hip arthroscopy.

Diagnosis

There is an insidious onset of pain typically at the groin but can also manifest at the buttock, lateral or anterior thigh, and low back. Common complaints include a reduced range of motion and /or pain in internal rotation and flexion with activity or trying to sit. Patients will state that they need to frequently change positions to alleviate pain. Diagnosis is usually delayed by years 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 early OA due to abnormal abutment forces on the acetabular labrum.

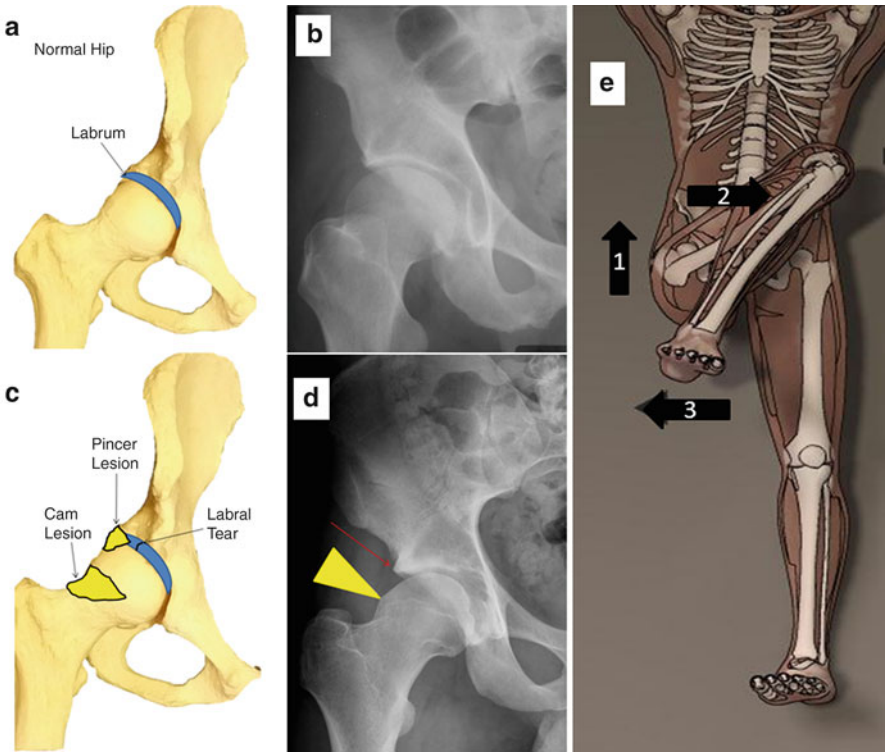

Fig. 2 Femoroacetabular impingement and FADIR test. (**a**) Normal hip anatomic model. (**b**) Normal hip AP radiography. (**c**) Hip anatomic model with cam and pincer lesion and labral tear. (**d**) AP radiography with cam lesion (*yellow arrowhead*) and pincer lesion (*red arrowhead*). (**e**) FADIR test: flexion (*arrow #1*), adduction (*arrow #2*), internally rotate (*arrow #3*) (FADIR image adapted with permission from fpnotebook.com)

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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 [7]. 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 (hip **f**lexion to 90°, **ad**duction, and **i**nternal **r**otation or FADIR; 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, radiographic confirmation is required. Plain radiography includes both a standing pelvis AP and a lateral view (frog leg, cross-table lateral) and possibly a Dunn view (AP pelvis with the hip at 20° abduction and either 45° or 90° flexion) to evaluate femoral head/neck morphology. Plain MRI has little role in FAI evaluation, but MR arthrogram can serve two purposes. The contrast material can help identify chondral and labral lesions which have important treatment implications. In addition the intra-articular anesthesia injected for the procedure can serve a diagnostic role in elucidating if the hip joint is the source of pain. CT is better at defining the three-dimensional bony abnormalities but should be ordered by the treating surgeon for surgical planning. The differential diagnosis includes tendinopathies and chondral or labral pathologies (see Table 1).

Treatment

A trial of nonoperative activity modification, hip strengthening, and pain control either orally or via intra-articular injections may be beneficial. 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 [8]. (This reference contains examples of home exercise handouts for a variety of conditions and is suggested for prescribing home rehabilitation therapy.) Nonoperative management is usually unsatisfactory for active adults as they often are not willing to discontinue/modify pain producing activities. Delayed intervention may also lead to degenerative joint disease which portends a poor prognosis and limits surgical options; therefore, referral is warranted once the diagnosis is made [7].

Greater Trochanteric Pain Syndrome (GTPS) or Trochanteric Bursitis

General Principles

GTPS is a common overuse syndrome involving the gluteus medius and minimus muscles, tendons, and bursa (see Fig. 1). These muscles' primary action is hip abduction. There are at least two involved bursas, the gluteus medius and trochanteric bursa. Bursas are small synovial lined structures that help tissues glide over one another, as when a tendon slides over another tendon or bone.

Overuse syndromes usually involve a victim and a culprit. The victim represents the presenting pain complaint which is the result of the culprit, the biomechanical dysfunction that created the victim. Successful treatment comes from correcting the culprit, not just treating the symptoms of the victim. In the case of GTPS, weakness of the gluteus medius and minimus muscles (the culprit) leads to abnormal hip and knee kinematics concentrated over the greater trochanter [9]. The body tries to alleviate this

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abnormal force by enlarging the bursas as a cushion. Bursa enlargement causes irritation and pressure and thus a painful trochanteric bursopathy develops (the victim). This similar pattern is seen with almost all overuse syndromes and the construct of victims and culprits should serve for treatment recommendations: alleviate the pain of the victim but search for and correct the culprit [10].

Diagnosis

GTPS is characterized by painful swelling and tenderness over the bony prominence of the posterior lateral thigh. Patients of all ages are affected, but the peak incidence is those aged 40–60. Pain may start after a specific trauma or have an insidious onset. Patients will 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 occasionally down to the calf and is exacerbated by prolonged standing, leg crossing, or single-legged activities. Repetitive hip internal or external rotation can also exacerbate symptoms [9].

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 physical exam should assess for malalignments of the lower extremity as mentioned earlier, gluteus medius weakness, and inflexibility of the iliotibial band. Pain on direct palpation is the most sensitive and specific finding. Often the culprit is a gluteal insertional tendinopathy (a disease of the tendon). 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).

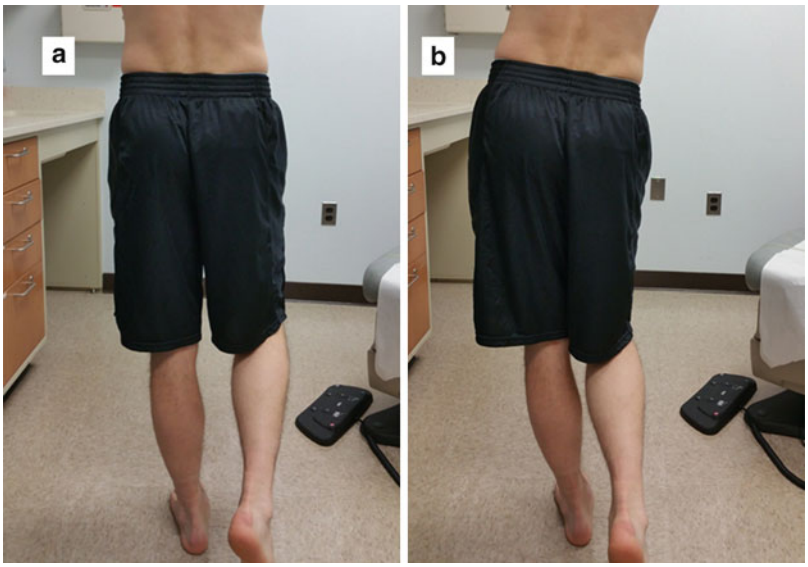

Fig. 3 Trendelenburg sign – patient stands on affected leg and lifts the unaffected leg from floor. (**a**) Normal response – ability to maintain pelvis in neutral position. (**b**) A positive or abnormal sign manifested by inability to maintain neutral posture when standing on the affected leg (non-weight-bearing hip will drop below the weight-bearing hip)

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GTPS is a clinical diagnosis. Imaging is pursued when the diagnosis is 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 is emerging as a cost-effective, readily available, and easily applied imaging modality that can show the same features. In addition, it can be used for dynamic assessments and to guide diagnostic and therapeutic procedures [9].

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. [8] for home exercises), and correction of any contractures. Weight loss is appropriate if indicated and can dramatically improve pain. (This holds true for all lower extremity conditions.) Interventions to relieve pain are required if pain precludes daily activities, sleep, and/or participation in rehabilitative exercises. 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 [9]. They should be considered when pain and dysfunction persist despite appropriate rehabilitation. These treatments should be done in conjunction with strengthening and stretching. Low-frequency shock wave therapy has shown conflicting results but may be an option [11]. Surgical treatment consisting of bursectomy is an option for the rare patient who is compliant with multiple courses of conservative therapy but who still is symptomatic.

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. ALTs are both common as well as frequently asymptomatic. A cadaveric study found that 93–96 % of hips [12].

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. ALT are undiagnosed for an average of 2 years owing to their vague pain pattern and lack of distinct physical exam techniques [12].

Diagnosis

The signs and symptoms of an ALT include anterior groin pain that worsens with anything that loads the joint such as prolonged periods of standing, sitting, or walking. Sharp pain often accompanied by mechanical symptoms such as clicking or catching is frequently described. Patients often state that they have trouble with sitting positions or when donning their socks and experience an exacerbation of their symptoms with sporting activities [12]. When patients are asked to point to the spot that hurts, they will cup the hip with their forefinger and thumb, dubbed the “C” sign.

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Hip examination must include a visual inspection for lower extremity malalignments, points of tenderness, range of motion, motor strength, and special tests. The special test for ALT with the most substantiating evidence the supine impingement test (FADIR test) described earlier (see Fig. 2). Other tests have been described but lack the supporting evidence of utility.

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) and a lateral projection of the symptomatic hip. 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) [13].

MRI with contrast is the imaging modality of choice and can demonstrate a displaced labral flap or irregular labral morphology. A paralabral cyst (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 [13]. The differential diagnosis (Table 1) includes tendinopathies and chondral lesions.

Treatment

A trial of conservative management, including relative rest and oral analgesic medications, combined with a focused PT protocol for 10–12 weeks is recommended. Therapy should focus on strengthening the hip, pelvis, and abdominal core musculature in addition to addressing flexibility deficits (see Ref. [8] for home exercises). A trial of intra-articular injection with steroid, prolotherapy, or PRP can be offered, but there is insufficient evidence to make a definitive recommendation at this time. In the case of steroids, repeated injections may damage chondral surfaces and are not recommended [11]. When conservative measures do not control the patient's symptoms or when functional limitations remain unsatisfactory, a referral for orthopedic surgery is appropriate [12].

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. Injury prevalence is 15–20 % for soccer and football players and 50 % for dancers [14]. The quadriceps muscles are the primary knee extensors and are made of the rectus femoris and vastus lateralis/intermedius/medialis. 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, 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. The rectus femoris and bicep femoris are biarticular muscles (span two joints) and thus are more prone to injury. The onset of injury is critical in differentiating between acute and chronic injury and likewise treatment recommendations.

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Diagnosis

Contusions will be the result of a direct blow or fall while tears/strains usually occur with bursts of speed/kicking/stretching and 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). Direct palpation and knowledge of muscle/tendon locations elucidate the structures injured. Pain at the bony origin raises the suspicion of an avulsion injury, while most strains occur at the tendo-muscular junction. Range of motion should be gently assessed and, in the acute setting, passive range of motion should not be attempted. Strength testing of the involved muscle unit will usually be diminished, and 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 needed for refractory cases or when the diagnosis is in question. Large contusions can lead to the development of myositis ossificans (MO), a calcification of a hematoma. MO presents 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.

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 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 [14]. 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 MO [14]. Once full range of motion is achieved, then strengthening should commence (see Ref. [8] 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.

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 sprinting, and type 2 occurs at the ischial tuberosity at the origin of the semimembranosus [15] (see Fig. 1). The rehabilitation is similar but type 1 injuries recover quicker compared with type 2 injuries and patients should be advised as such. Rehabilitation begins with restoring full range of motion and then progresses to regaining strength and then ultimately activity- or sport-specific drills (see Ref. [8] for home exercises). The use of a thigh compression sleeve is recommended in the acute, chronic, and rehabilitative setting. These injuries are very prone to recurrence and 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 the "► Athletic Injuries" chapter. They require addressing risk factors (see Table 2), biomechanical assessment, and strengthening of the involved muscle groups as well as the core muscles.

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Knee Injuries

Meniscal Injuries

General Principles

While its use has decreased over the last 15 years, arthroscopic partial meniscectomy (APM) is still the most common orthopedic surgical procedure in the United States with reported annual incidence rates of 66/100,000 [16]. 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.

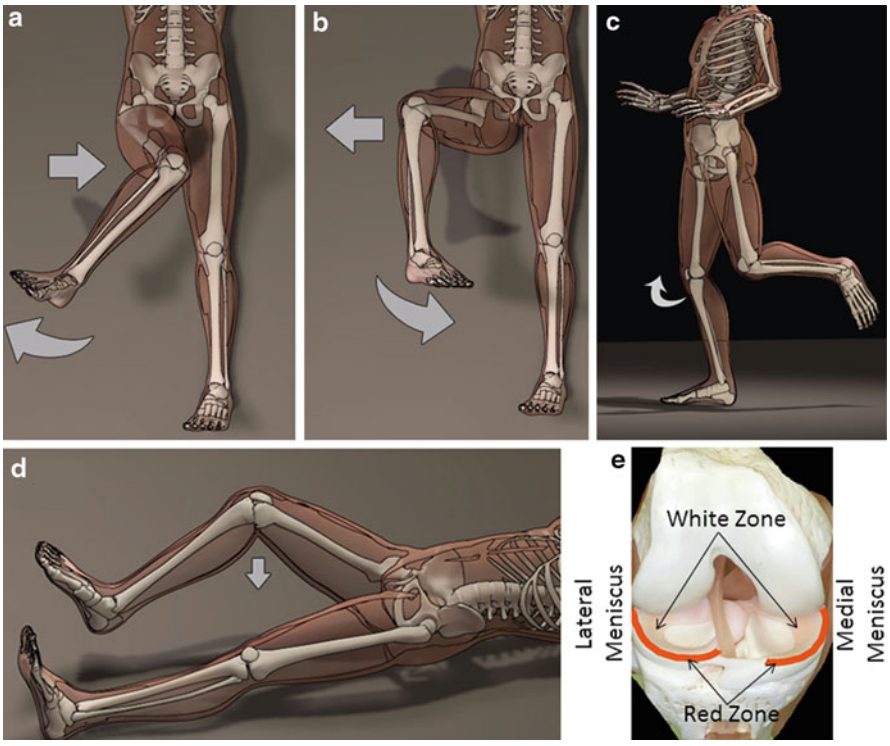

Fig. 4 Meniscal signs and anatomy. (**a**) McMurray test for medial meniscus – with fingers on medial and lateral joint line, flex the hip and knee maximally. Apply a valgus force (in direction of *straight arrow*) to the knee while externally rotating the foot (in direction of *curved arrow*) and passively 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)

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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 [17].

Diagnosis

Acute meniscal injuries present after a traumatic event. This can be a sudden noncontact twisting event (the most common mechanism) or through 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 [16]. 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.

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 [18]. 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 [17].

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.

A randomized clinical trial 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 years of follow-up [19]. Similar results have been found by other researchers and support the option of conservative management of degenerative tears without true mechanical symptoms.

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Table 4 Knee and calf differential diagnosis 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 solues 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

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 [20].

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Diagnosis

Patients generally complain of fullness behind the knee and a mass can usually be seen and 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).

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 [21]. 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.

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, switch order as it reads funny with the editing/line justification. 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 [22]. 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: [22]

- 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.

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- 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 [23]:

- 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)

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).

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 [23].

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

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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 [24]. 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 [24]. 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 comanaged 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. Adolescents with stable lesions can heal, but the skeletally mature are very unlikely to heal on their own [25].

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 medial facet of the patella. 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 radiographically in all cases.

Lower Leg/Ankle/Foot Injuries

Calf Injuries

General Principles

Injuries to the posterior lower leg (calf) are very common especially in the 40–60 year age group [26]. The muscles involved are the gastrocnemius and soleus (also known as the triceps surae as some anatomists believe, this is one muscle with three heads and a common insertion point on the posterior calcaneus, the

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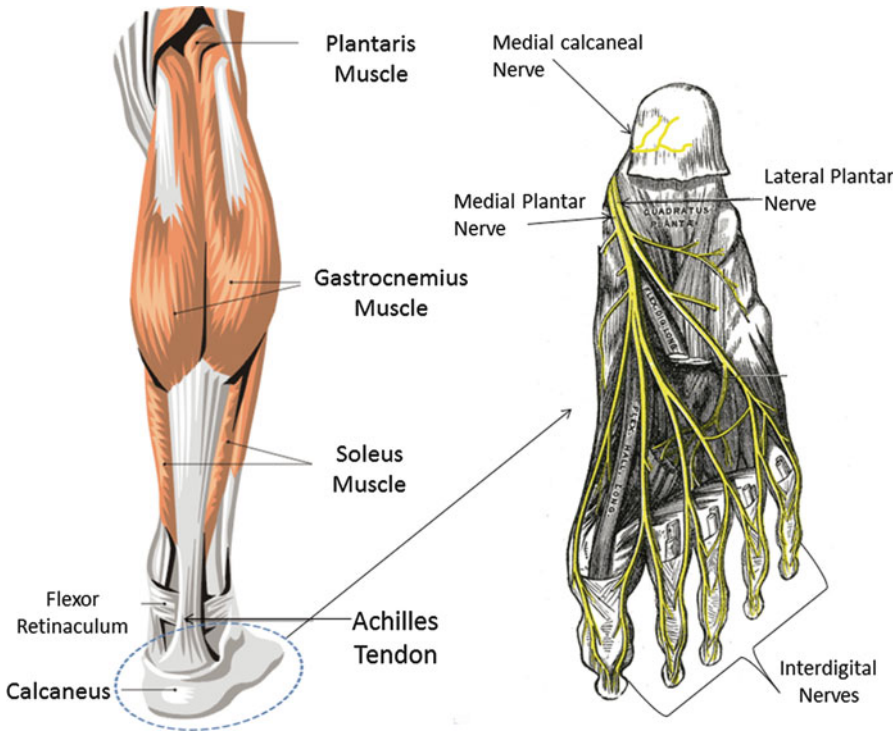

Fig. 5 Posterior distal leg and plantar foot anatomy (distal leg image adapted with permission from fpnotebook.com). Plantar foot adapted from Gray's Anatomy 20th edition from 1918 (Lewis) in the public domain following expiration of its patent. Available online at http://bartleby.com/107/)

Achilles tendon) and the plantaris (see Fig. 5). Together these muscles are the primary plantar flexors of the ankle. Most injuries occur with sudden explosive movements or prolonged running activity. The gastrocnemius is another biarticular muscle of the lower extremity and is composed of a medial and lateral head originating on the respective femoral condyles. The soleus has a broad origin on the proximal tibia and fibula. Over 90 % of injuries involve only the gastrocnemius muscle (medial head 80 % and lateral head 14 %). The plantaris muscle is highly variable in its actual presence and exact location. When present, it originates just medial to the lateral head of the gastrocnemius and is situated just between the gastrocnemius and popliteus muscles proximally and the gastrocnemius and soleus muscles distally. Although its function is debated, it is important to note as injury to the muscle/tendon must remain in the differential of calf pain. The popliteus muscle originates from the lateral posterior complex 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 [27].

Diagnosis

Gastrocnemius injuries are generally of acute origin as when sprinting or jumping such as a tennis player trying to return a shot (hence the moniker "tennis leg"). Pain can be described as a tearing or popping sensation and most will have difficulty bearing full weight on the injured leg. As mentioned earlier, the site of the injury is usually the medial head of the gastrocnemius. There may be a variable amount of swelling or bruising depending on the degree of muscle injury. Active plantar flexion will be painful as this engages the muscle, while passive dorsiflexion will be painful as this stretches an already damaged muscle. The most immediate condition to rule out is an Achilles tendon tear. Both have similar mechanisms of injury but are readily differentiated by physical exam and imaging when necessary. The integrity of the Achilles

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tendon should be assessed with careful palpation. With a tear, there will be considerable swelling at the tear site and a defect can usually be appreciated. There may be lack of passive plantar flexion with the squeezing of the proximal calf musculature while the patient is prone, also known as the calf or Thompson squeeze test. The nomenclature can be confusing as a negative squeeze test is when there is plantar flexion indicating an intact muscle-tendon complex and a positive test is when there is no plantar flexion, indicating a disruption of the muscle-tendon complex. It is less confusing to describe the motion observed when squeezing the posterior calf as opposed to saying a negative or positive test [28]. Due to the plantaris muscle/tendon and deep toe flexors, some passive plantar flexion may still be present even in up to 10 % of complete Achilles tendon ruptures [27]. Likewise, the lack of any passive plantar flexion does not always mean a complete tear either. Two case reports are documented where a positive calf squeeze test (no movement of the ankle) was noted, and upon surgical evaluation, only a tear of the gastrocnemius component of the Achilles tendon was identified with an intact soleus component [29]. Should clinical suspicion still exist for an Achilles tendon tear, imaging either with ultrasound or MRI should be pursued. Ultrasound is quicker and less expensive but is operator dependent, and occasionally an intact plantaris tendon can be mistaken for an intact Achilles tendon, and a large hematoma may obscure complete examination. Both modalities can also be used to evaluate for other clinical entities.

Plantaris injuries, to include muscle or tendon tears, are also of acute origin with the same mechanism as gastrocnemius injuries. Symptoms are similar but not as severe. Due to the plantaris muscle tendon lying underneath the gastrocnemius, swelling and bruising are not as apparent. In addition, these injuries are more distal than the typical medial head gastrocnemius injuries and are usually located mid-calf. The Achilles tendon will be non-tender and intact along its length. As the plantaris usually does not contribute to the Achilles tendon, the calf squeeze test will show ankle plantar flexion (a negative test).

Contrary to gastrocnemius and plantaris muscle injuries, soleus muscle injuries are usually chronic in nature. This may be due to their muscle fiber type. The gastrocnemius is comprised of both fast and slow twitch fiber type while the soleus is comprised almost solely of slow twitch muscle fibers. Distance runners and those who engage in hill running are especially vulnerable to soleus injuries. There is no significant swelling or bruising and palpation only reveals deep muscle soreness. A clue to the diagnosis is to functionally test the soleus muscle. This can be accomplished by having the patient do multiple heel raises on a step (active plantar flexion) with the knee bent to 20–30° of flexion. The gastrocnemius is tested with the knee in full extension. Pain while the knee is flexed but reduced or absent with knee extension is highly suggestive of a soleus muscle injury.

A complete evaluation should include an examination of the entire kinetic chain as mentioned earlier in GTPS by specifically looking for leg length discrepancies, foot abnormalities (pes cavus or pes planus), or hip weakness as evidenced by a positive Trendelenburg sign (see Fig. 3). Table 4 provides a differential diagnosis for lower leg complaints.

Treatment

Treatment is undertaken in a phased approach similar to the majority of all muscle-tendon injuries. (A detailed description will follow and will serve as a model for other muscle-tendon injuries, i.e., groin, quadriceps, and hamstring injuries.) The initial phase is centered on protecting the injury from further damage while trying to restore range of motion. Calf compression can be helpful and is accomplished with commercial compression sleeves or elastic bandages; the latter may be more prudent acutely if a large amount of swelling is present in order to adjust tightness as needed to avoid compression of neurovascular structures. Ice is generally suggested for acute injuries and pain medication (acetaminophen or NSAIDs) can be used as necessary. Severe injuries occasionally require immobilization either with a posterior splint or a commercial walking boot. The continued need for immobilization should be revisited every 3–5 days as normal range of motion is one of the early treatment goals. Some advocate a heel lift to shorten the

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muscle-tendon unit and relieve pain. 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, the ability to do a heel lift should be tested. If this can be done with minimal pain, the patient may begin active rehabilitation that consists of strengthening the gastrocnemius-soleus complex with repetitive heel raises and progressive loads (see Ref. [8] for home exercises). Sport-/activity-specific training can begin after the patient can tolerate multiple sets of heel raises. Every patient is variable and rather than exact timeframes, functional assessments should be used to guide treatment advances: 1, ability to walk without a limp; 2, ability to do heel lifts without significant pain; and 3, pain-free functional activity.

The continued use of a calf compression sleeve is an option and patient dependent. To prevent recurrences, 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/planus.

Achilles Tendon Rupture

General Principles

The Achilles tendon, the attachment point of the gastrocnemius-soleus muscles to the posterior calcaneus, has poor vascularity 2–6 cm prior to its insertion (see Fig. 5). This area is most at risk for both tendinopathies and rupture. The annual incidence of rupture is 8/100,000 in the general population but up to 8/100 in the athletic population [30]. Males in their 40s represent the largest cohort. The mechanism of injury is the same as for acute calf injuries described above: a quick change of direction while the ankle is dorsiflexed and the calf muscles contract vigorously either in sporting events or from a fall/misstep. Approximately 10 % of patients who sustain an Achilles tendon rupture had preexisting Achilles tendon problems. The use of fluoroquinolones only slightly increases the risk of tendon ruptures (and tendinopathy) from an unknown mechanism [31]. This risk exists only with the first exposure and is highest for the initial 30 days. Subsequent use does not seem to carry any increased risk. Corticosteroid use also increases the risk for all tendon injuries; the exact increase is unknown.

Diagnosis

An oft-heard complaint is “someone kicked me in the back of the leg.” An audible snap is not uncommon. Plantar flexion is greatly diminished while dorsiflexion is maintained [32]. Most complain of intense pain, but a case series reported that up to one third of patients had no pain with the acute rupture [33]. It is speculated that these patients had chronic tendinopathy and the rupture actually relieved some of the discomfort from the tendinopathy. There is usually a great deal of swelling and ecchymosis in the acute setting. Careful palpation of the tendon will reveal a gap but can be obscured due to the inflammation. In addition to palpation of the tendon, the entire calf musculature should be examined as above because the differential diagnosis is gastrocnemius, soleus, or plantaris injury (see Table 4).

Strength testing demonstrates markedly decreased plantar flexion. The calf squeeze test described above usually shows no plantar flexion (a positive test). As mentioned earlier, even in the face of a complete rupture, there may still be some plantar flexion, and on the corollary, loss of plantar flexion is not 100 % sensitive or specific for a complete rupture. For these reasons and others, it has been estimated that ruptures are missed up to 25 % of the time. Note that these estimates were made prior to the widespread availability of ultrasound and MRI. These advanced imaging studies should be done whenever there is any doubt about the integrity of the tendon, as missed ruptures have high morbidity.

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Treatment

The treatment of Achilles tendon ruptures was traditionally surgical for the active population and nonoperative for the elderly or those with major comorbidities. Recent studies have challenged this notion, and coupled with modern rehabilitation techniques, nonoperative treatments remain a viable option even for the active patient. Joint decision making is paramount. Nonoperative treatment includes a progression from non-weight-bearing casting to a walking boot to a heel wedge with clinical and radiographic assessment of tendon integrity along the way [34]. Physical therapy is performed in conjunction. Unless the physician has considerable experience in managing Achilles tendon ruptures, to include serially casting/splinting, referral to an orthopedic surgeon is recommended. Most authorities still advocate surgical repair for the very active population though [35]. To avoid recurrence regardless of intervention, patients should maintain proper strength and flexibility and consideration should be made to avoid sudden ballistic movements in at-risk population.

Plantar Fasciopathy (PF)

General Principles

Plantar fasciopathy (also known as plantar fasciitis) is the most common cause of heel pain in adults affecting more than two million annually in the United States. The peak incidence is between the ages of 40 and 60 [36]. Those at higher risk include runners and occupations that involve 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 many structures of the foot. Originating on the planar aspect of the calcaneus, the plantar fascia consists of medial, central, and lateral bands. The central portion is most often involved in PF and divides into five bands inserting on to the metatarsophalangeal joints. Its main function is to provide both static and dynamic support of the longitudinal arch.

Biomechanical dysfunction leading to micro-tears at the calcaneal enthesis is thought to be the etiology. The histopathology of PF reveals degenerative tissue and a lack of inflammatory cells which is why the term fasciitis is incorrect. This lack of inflammatory cells also has implications on treatment as well [37]. Enthesopathic conditions such as the seronegative spondyloarthropathies can also present with pain at the plantar fascia. In these cases, inflammation is present due to an autoimmune inflammatory process and not a degenerative process and truly does represent a true plantar fasciitis.

Diagnosis

The classic history is pain which is worst upon the first steps after sleeping or prolonged sitting, improving or at least diminishing in severity after a few minutes of ambulation. There usually is no radiation and if present should alert one to an alternative diagnosis, such as a nerve compression. An inspection of the entire lower extremity should be done as mentioned previously looking for any mal- or misalignments but specifically for leg length abnormalities (true or functional) and foot abnormalities (pes cavus or planus) (see Table 2). There generally is no appreciable swelling or bruising, and their presence would suggest another entity other than PF. Physical exam findings include sharp pain and tenderness over the medial plantar calcaneal region that is accentuated with great toe extension or ankle dorsiflexion. Ankle dorsiflexion may be limited and one must try to deduce if this is from pain or if the Achilles tendon complex is the cause of the limited dorsiflexion which leads to greater stress on the plantar fascia. Palpation and percussion of the posterior tibial nerve, especially the media calcaneal and lateral plantar branch, should be done to ensure they are not the source of the pain (see Fig. 5).

PF is a clinical diagnosis and imaging is reserved to rule out other conditions. The presence of a bony heel spur is fairly meaningless. It is not the cause of the symptoms, although it may be the result of the

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Table 5 Ankle and foot differential diagnosis disorders of the lower extremity

Very common	Common	Infrequent	Referred
Ankle sprain	Achilles tendon rupture	First MTP joint sprain (turf toe)	Radiculopathy
Plantar fasciopathy	Fractures	Calcaneal abnormalities (retrocalcaneal, Haglund)	Chronic regional pain syndrome
Tendinopathy[a]	Metatarsalgia (multiple causes)	Enthesopathies of autoimmune conditions	Septic arthritis
Stress fracture	Toe abnormality[b]	Fat-pad atrophy	Neoplasm
Osteoarthritis	Hallux valgus	Nerve compression[c]	Vascular disorders
	Interdigital nerve entrapment	Osteochondrosis[d]	
	Corns/calluses	Hallux rigidus	
	Sesamoid disorders	Lisfranc injury	
		Plantar fascia rupture	
		Cuboid subluxation	
		Plantar fibromatosis	
		Sinus tarsi syndrome	
		Tarsal coalition	

[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)

body reacting to the stresses at the calcaneal plantar fascia origin [36]. The most common mimickers are fat-pad syndrome and neuropathies, but it is possible to have multiple concurrent pathologies and one may beget the other [38] (see Table 5 for differential diagnosis).

Treatment

The natural history of PF is self-limited resolution in >95 % of patients but may take up to 12 months [37]. There are a myriad of potential treatments with limited evidence as well as conflicting and mixed results. Therefore a conservative, least invasive, least costly approach is prudent. Obesity is an extrinsic risk factor for all musculoskeletal conditions and should be addressed. If training errors are revealed, these should be corrected. If clues to biomechanical dysfunction are discovered, these should be corrected as well (i.e., lower extremity/core weakness, leg length abnormality, pes cavus/planus; see Table 2). The use of foot orthoses is recommended by many. Unless the patient has true pes cavus, a prefabricated foot insert will suffice for the majority of patients [39]. 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 main goal. This can be accomplished with ice massage, pain medications (oral, topical, or injections), and foot orthoses. As soon as tolerated, the stretching and strengthening of the foot and lower extremity complex should proceed. In addition to stretching the plantar fascia itself, the Achilles tendon complex should be stretched repeatedly throughout the day (see Ref. [8] for home exercises). Dropping below the parallel while standing on a step with just the toes can stretch both structures and is also a form of eccentric strengthening exercise [40]. (Eccentric strengthening is when the muscle tendon is contracting while lengthening as in deceleration or lowering a weight.) Orthoses for PF can be heel cups/cushions, counterforce braces, sock-like sleeves, shoe inserts, or dorsiflexion splints. No good evidence-based recommendations can be made, but some patients improve dramatically with their use [39]. They should not be used in isolation but as part of a comprehensive treatment regimen that must include stretching, strengthening, and correcting any extrinsic risk factors discovered.

For refractory cases, injections can be pursued. Corticosteroid/anesthesia injections can provide immediate relief and help to confirm the source of pathology. Their repeated use is discouraged for risk

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of fat-pad atrophy or plantar fascia rupture. In general, they should be employed when severe pain limits ADLs or prohibits rehabilitation. Prolotherapy, PRP, and botulinum toxin are advocated by some and remain an option for recalcitrant cases. Low-frequency shock wave therapy treatments are also employed when other measures fail, but results of trials are mixed [11]. Surgery is a last resort and the diagnosis must be revisited if the patient is not responding to appropriate treatment.

Metatarsalgia

General Principles

Metatarsalgia literally means pain at the metatarsals. It is a nonspecific term applied to any painful condition around the forefoot, generally the metatarsal heads. It is more of a symptom rather than a condition and treatment rests in elucidating and ameliorating the cause of the symptom (victims and culprits concept discussed in GTPS). Forty percent of impact forces are born by the first digit; any condition that alters this normal force distribution is a contributor to the condition. Although any and all of the distal metatarsals can be involved, the second metatarsal head is affected more often due to its relative inflexibility compared with the other digits, its proximity to the main force absorber (the first digit), and the not uncommon anatomic variation of a shortened first metatarsal (the so-called Morton's toe or Morton's foot) [41]. The following section will discuss in greater detail the more common entities that the family physician will encounter that cause metatarsalgia. A more extensive list of causes is provided in Table 5.

Diagnosis

The history is one of gradual pain without overt trauma. An occupational history is paramount as this may be a major modifiable risk factor. As in all musculoskeletal examinations, inspection of the entire kinetic chain should take place looking for any obvious abnormalities. Stress fractures are in the differential diagnosis so inquiring about recent change in exercise pattern is required (see Table 2 for risk factors).

Local tenderness to palpation over the plantar metatarsal heads is present. Weight-bearing plain radiographs may be ordered to assess for additional bony pathology. Advanced imaging with ultrasound and MRI can be used to evaluate for other entities (stress fractures, nerve impingement, etc.). Salient findings for specific diagnosis will be discussed under their respective section.

Treatment

Successful long-term treatment resides with elucidating the cause of the 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 obvious anatomic changes, a custom foot orthoses can be pursued [41].

Interdigital Nerve Compression

A variety of conditions can cause compression with subsequent swelling of the interdigital nerves of the toes (see Fig. 5). Morton's neuroma (note there is no true nerve tumor and as such this is a misnomer) specifically refers to nerve compression between the third and fourth digits and is the most common site. Typical nerve paresthesia symptoms are present in the involved nerve distribution and can be accentuated with direct palpation. 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 and is called the Mulder's sign.

Symptomatic relief with an anesthesia block can be diagnostic and if combined with corticosteroid can be therapeutic as well. A dorsal approach is highly recommended to avoid complications and ultrasound guidance is advocated to ensure precise delivery under direct visualization [41]. Recurrence can be treated with either nonsurgical (i.e., alcohol) or surgical nerve ablation techniques, but successful long-term

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management also includes correction/management of the biomechanical deformities causing the nerve compression.

Sesamoiditis

Sesamoiditis is also a generic term for pain located around the sesamoid complex. The sesamoid complex is the main force absorber 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 flexion power of the MTP joint and to absorb the majority of weight bearing along the medial aspect of the foot. Either sesamoid can be bipartite and patients with pes cavus are at higher risk for sesamoid injuries [42].

Patients will present with pain directly over the involved sesamoid upon palpation and great toe dorsiflexion. Various types of padding (i.e., dancer's pad) and foot orthoses are used for treatment but the basic concept is to redistribute the force. Imaging is not required unless it will change management as treatment is centered on correcting any biomechanical dysfunction in order to off-load the force at the sesamoid. If the diagnosis is in question or the patient is not responding to conservative treatment, plain films including an axial sesamoid view should be ordered but can be difficult 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 (turf toe). Turf toe is an acute injury that can be recalcitrant to healing as it is difficult to fully unload. It is treated with rest and custom orthoses.

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 "► Athletic Injuries" chapter. 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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Family Medicine
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Osteoarthritis

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1 General Principles

1.1 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].

1.2 Epidemiology

OA is one of the most common chronic medical conditions and the most common type of arthritis [1]. In 2005, the Centers for Disease Control reported that 13.9 % of adults aged 25 and older and 33.6 % (12.4 million) of those 65+, an estimated 26.9 million, US adults have OA [3]. OA accounts for 69.9 % of all arthritis-related hospitalization, and in 2006 approximately 814,900 hospitalizations were for OA as the principal diagnosis [3]. Estimated costs from hospital expenditures of total knee and hip joint replacements are approximately $28.5 billion and $13.7 billion, respectively, in 2009 [3]. The annual direct and indirect cost of OA per patient in 2000 was $5700 [3]. Risk factors include genetics, acute or recurrent trauma, advancing age, female gender, and obesity [4].

1.3 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.

1.4 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 (Table 1). Using these criteria, there is a sensitivity of 95 % and specificity of 69 % in diagnosing OA [5].

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Table 1 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

Table 2 Hand osteoarthritis classical clinical criteria [6]

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

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].

1.5 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) (Table 2). These criteria accurately diagnose OA with a sensitivity of 89 % and specificity of 91 % [6].

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].

1.6 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 (Table 3). These traditional inclusion criteria yielded a sensitivity of 94 % and specificity of 87 % [7].

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Table 3 Hip osteoarthritis classical clinical criteria [7]

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)

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].

2 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.

3 Diagnosis

3.1 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 with symptoms to include pain, limited morning stiffness, and reduced function [8].

3.2 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.

3.3 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 [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 sunrise views should be ordered. For the evaluation of hip/pelvis OA, an anteroposterior weight-

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Table 4 X-rays for osteoarthritis [11]

Knee	Anteroposterior weight bearing, lateral, sunrise
Hip/pelvis	Anteroposterior weight bearing
Spine	Anteroposterior, lateral
Hand	Anteroposterior, oblique, magnified view
Foot	Anteroposterior, lateral, oblique, magnified view

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 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 4) [11].

3.4 Differential Diagnosis

The differential diagnosis for OA includes crystal-induced arthritis, gout, pseudogout, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, septic joint, and Lyme disease.

4 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.

4.1 Lifestyle Modifications

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].

5 Medications

5.1 Acetaminophen and Anti-inflammatories

Oral medications are the mainstay treatment used to treat OA [1]. Acetaminophen is the first-line treatment in patients older than 65 years and the preferred agent due to the greater safety profile when compared with the use of nonsteroidal anti-inflammatory drugs [15]. Acetaminophen should be started initially on an as-needed basis, but in patients with persistent symptoms, regular use may be initiated at doses up to 3 g/day [16]. 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,

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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 (NSAIDs) are recommended when acetaminophen does not adequately relieve pain. NSAIDs 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 [17]. Inhibition of the COX-1 enzyme is responsible for the associated gastrointestinal toxicity [17]. 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 [18]. A short to medium acting NSAID is generally used on an episodic basis in patients with noninflammatory 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.

COX-2 inhibitors were developed to provide relief of pain without associated gastrointestinal complications; however, COX-2 inhibitors have a similar risk of serious adverse gastrointestinal effects as other NSAIDs in long-term users [17]. Chronic use of COX-2 inhibitors has also been associated with an increased cardiovascular risk [17]. Consider treating gastrointestinal symptoms associated with NSAID use with antacids, H2 blockers, or proton pump inhibitors. In patients being treated chronically with daily NSAIDs, consider obtaining a complete blood count, blood urea nitrogen, creatinine, and aspartate aminotransferase.

5.2 Topical Medications

Topical NSAIDs or capsaicin can be used as an alternative treatment in patients who cannot tolerate oral agents, have contraindications to oral agents, or those that may have an increased risk of adverse side effects. Topical NSAIDs typically 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 [19]. Capsaicin has shown mild to moderate efficacy in randomized trials in hand and knee OA in comparison with placebo [20].

5.3 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 [21]. Corticosteroids are proven to be effective at reducing pain in knee OA, although duration and exact efficacy of these treatments is controversial [2]. Corticosteroids decrease pain by roughly one third but provides that benefit for approximately 1 week [2, 21]. A dose equivalent to 50 mg of prednisone may be required to show benefit at 16–24 weeks [21]. The ACR suggests that a dose of 40 mg triamcinolone be used for injections to provide adequate pain relief [21]. 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 [21]. 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 [22]. In a Cochrane review, hyaluronic acid and hylan products were

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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 postinjection period. In some analyses, viscosupplements were comparable in efficacy to systemic forms of treatment but with more local reactions and fewer systemic side effects [23]. The use of these medications remains controversial.

5.4 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 [24]. Adverse events were not shown to be life threatening, and the drug may have had some synergistic effect with acetaminophen [24]. It is recommended that non-tramadol opiates not be routinely used due to the increased risk for adverse events [25].

5.5 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 [26].

5.6 Complementary and Alternative Therapy

Controversy exists about the effectiveness of glucosamine. 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 [27, 28]. 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 [27].

Other complementary therapies such as chondroitin, ultrasound therapy, acupuncture, magnet therapy, ginger, avocado/soybean unsaponifiables, leaches, laser light therapy, platelet-rich plasma, dextrose prolotherapy, tai chi, balneotherapy, and ice massage may be helpful in treating OA but there is limited evidence [29–41].

5.7 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 [42]. Arthroscopy with arthroscopic debridement and lavage is not an effective treatment for OA of the knee [43]. In one randomized control trial (RCT), arthroscopic surgery plus medical and physical therapy was no more effective than medical and physical therapy alone [44]. Obese patients with BMI >30 are no longer considered as great a risk of hardware failure after total joint replacement as previously thought [42].

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.

5.8 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

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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.

5.9 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 $\geq$10 (a scoring system developed to assess severity of OA, $\geq$10 is considered severe) [45].

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Family Medicine
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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 6 weeks). Accurately diagnosing the cause of joint pain, encouraging continuity of care, and working with multidisciplinary teams using the right blend of therapeutic modalities gives 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 (tendionopathy, bursopathy, enthesopathy). If the pain is more diffuse, systemic disorders come to mind. Is the pain symmetric? Rheumatoid arthritis, systemic lupus erythematosis, 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. Noninflammatory 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

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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.

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. 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. While time consuming, an accurate documentation of the physical examination, particularly the musculoskeletal exam, is important to assess changes over time. Fortunately, many electronic medical record systems have embedded templates for just this purpose. Formal dynamometry can be used to track changes in strength over time (e.g., grip strength). 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.

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 has recently been 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]. 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.

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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 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).

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 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]. 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

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Table 1 2010 ACR-EULAR classification criteria for rheumatoid arthritis

	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

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 [9].

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 include nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs) including biologics, corticosteroids, and biologic agents. Selecting the right therapy for the right patient to optimize outcome while minimizing toxicity can be challenging.

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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 [10]. 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 discussed with patients who are being considered for therapy with DMARD or biologic 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.

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 (TNF) 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 therapy should avoid live viral vaccines and should be screened for latent tuberculosis infection before initiating therapy.

Other non-TNF biologic DMARDs are available. These include rituximab (most often used in combination with MTX), anakinra, abatacept, tofacitinib, 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 a definition of remission of RA for use in clinical trials [12]. Patient activity scales, clinical disease activity indices, and composite scores are combined to determine low, moderate, or high disease activity. 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; 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 health care 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 is clinically important. Patients with RA typically

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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, hydroxycholoroquine, 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

complain of morning stiffness, whereas the pain associated with OA increases through the 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

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involved in OA. Soft tissue swelling and warmth are more common in RA. Plain films in RA show periarticular osteopenia and marginal erosions. 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. Recent 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 are 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, enthesis-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 [15]. 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 is 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 enthesis-related JIA additionally include restrictive lung disease and aortic insufficiency. Children with undifferentiated arthritis often have manifestations in multiple JIA categories.

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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 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 [16]. Current treatment regimens are available based on the following criteria: (a) history of arthritis in $\leq$4 joints, (b) arthritis in $\geq$5 joints, (c) active sacroiliac arthritis, (d) systemic arthritis (inactive), (e) systemic arthritis (active). The first group ($\leq$4 joints) generally includes patients with psoriatic arthritis, enthesis-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 $\geq$5 joints (RF-negative/RF-positive polyarthritis, psoriatic arthritis, enthesis-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 are 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 Syndrome)

Reactive arthritis (formerly known as Reiter's syndrome) is an autoimmune response to infection associated with multiple gastrointestinal (GI) and genitourinary (GU) species [17]. *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 psoriaform 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 [18]. 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 [19]. While NSAIDs are frequently used as initial therapy, sulfasalazine, methotrexate, and anti-

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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.

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, 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). The presence of 4 of the 11 ACR criteria has a 95 % specificity and 85 % sensitivity for the diagnosis of SLE [20].

History and physical examination. Fever, fatigue, and weight loss are the most common constitutional complaints in patients presenting 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 urticaria. 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 [21]. 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 1997 update of the 1982 American College of Rheumatology revised criteria for classification of SLE [20]

Criterion	Description
Four or more of the following 11 criteria (serial or simultaneous)	
Malar rash	Fixed erythema, flat or raised, over the malar prominences, tending to spare the nasolabial folds
Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
Photosensitivity	Skin rash as a results of unusual reaction to sunlight, by patient history or physician observation
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
Arthritis	Involving two or more peripheral joints characterized by tenderness, swelling, or effusion
Serositis	(A) Pleuritis: convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion *or*
	(B) Pericarditis: documented by electrocardiogram or rub of evidence of pericardial effusion
Renal disorder	(A) Persistent proteinuria >0.5 g/day or >3+ on dipstick *or*
	(B) Cellular casts: RBC, hemoglobin, granular, tubular, or mixed
Neurologic disorder	(A) Seizures: no potentially inciting drugs or known metabolic abnormality (electrolyte imbalance, renal failure) *or*
	(B) Psychosis: no potentially inciting drugs or metabolic abnormality
Hematologic disorder	(A) Hemolytic anemia- with reticulocytosis *or*
	(B) Leukopenia: <4,000/mm^3 total on 2+ occasions *or*
	(C) Lymphopenia: <1,500/mm^3 on 2+ occasions *or*
	(D) Thrombocytopenia: <100,000/mm^3 (no offending drugs)
Immunologic disorder	(A) Anti-DNA *or*
	(B) Anti-Sm *or*
	(C) Antiphospholipid antibodies (i) abnormal IgG or IgM anticardiolipin antibodies, (ii) positive lupus anticoagulant or (iii) a false-positive serologic test for syphilis
Antinuclear antibody	An abnormal antinuclear antibody (ANA) titer in absence of offending drugs

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 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. 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. Anticardiolipin antibodies and lupus anticoagulant testing are laboratory tests that can identify antiphospholipid antibodies that may be associated with the antiphospholipid antibody syndrome.

Treatment

The updated European League Against Rheumatism (EULAR) recommendations provide sound guidance for the treatment of SLE [22]. For patients who do not have major organ involvement, corticosteroids and antimalarials are helpful. Traditionally, hydroxychloroquine has been the cornerstone therapy for SLE

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to prevent flares and reduce disease mortality. Nonsteroidal anti-inflammatory drugs 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 and methotrexate are also useful for certain manifestations and control of systemic disease. Recently, the FDA has approved the monoclonal antibody belimumab in combination with standard therapy for treatment of SLE. Additional guidelines for the management of lupus nephritis were published by the ACR in 2012 [23].

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. Patients should receive annual influenza vaccine and should also receive the pneumococcal and meningococcal vaccines [24].

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 [25].

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 [24] 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 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 [26]. Nifedipine (30–120 mg

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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.

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 (*c*alcinosis, Raynaud's phenomenon, *e*sophageal dysmotility, *s*clerodactyly, and *t*elangiectasias) 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 [27], 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 results in organ dysfunction and clinical disease. While the exact etiology is not known, exposure to silica, solvents, and/or radiation in genetically susceptible individuals have all been hypothesized to trigger the disease [28]. 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 USA, the highest 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, pruriitis, 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 [29]. 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. Sildenafil has been approved to treat pulmonary hypertension. Bosentan (an endothelin receptor antagonist) has been approved to treat SSc-related pulmonary hypertension and may decrease digital ulcer formation. Antacids, histamine blockers (H2), and proton pump inhibitors can treat common reflux symptoms associated with SSc. Cyclophosphamide has been used to treat pulmonary fibrosis in patients with SSc.

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,

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Table 4 ACR/EULAR revised systemic sclerosis classification criteria [27]

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 phenomenon	None	3
Systemic sclerosis–related autoantibodies (*maximum score is 3*)	Anticentromere	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

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 American-European Consensus Group (AECG) criteria [30] for classification of Sjögren's syndrome include (a) ocular symptoms: dry eyes for >3 months; (b) oral symptoms: xerostomia, swollen salivary glands; (c) ocular signs: Schirmer's test <5 mm in 5 min); (d) oral signs: abnormal salivary scintigraphy, sialography, or sialometry; (e) positive salivary biopsy; (f) positive anti-SSA or anti-SSB antibodies.

Sjögren's syndrome is more common in patients with HLA-DR52 and affects women nine times more often than men [31]. 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 (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 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 are supportive of the diagnosis. Autoantibodies are common in Sjögren's syndrome with anti-SSA and

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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 cevimiline have been used for more severe cases of xerostomia [32]. If major organs are involved, the use of immunosuppressive therapy (cyclophosphamide), rituximab, or systemic corticosteroids is appropriate [33]. 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. Pathophysiologically, it 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 [34]. The median age at the time of diagnosis is 72 years. One in three patients with polymyalgia rheumatica also have temporal arteritis.

The predominant clinical features of PMR are pain or weakness of the hips and shoulders 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 new scoring criteria [35] 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), (d) no peripheral joint pain (1 point). 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. 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 15 mg/day. If a patient does not respond quickly 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 [36]. When attempts are made to wean a patient off prednisone, the dose is decreased by only 1 mg/month. Methotrexate and TNF-α inhibitors have also been used as steroid-sparing treatments for PMR [37].

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. Pathophysiologically, GCA is characterized by inflammation of the vascular wall of affected arteries (e.g., the temporal artery) resulting in endothelial injury, luminal narrowing, and distal ischemia. Like polymyalgia rheumatica, GCA typically presents in patients over 50 [38]. The incidence of disease peaks in the eighth decade of life. GCA is more common in women (3:1) and in whites of Northern European descent.

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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) [39]. The headache is most commonly tempuraoccipital 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 [40] and others [41] 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 $\geq$ 50 mm/h, (e) positive TAB (vasculitis with mononuclear infiltration). High-dose corticosteroid therapy is the cornerstone of therapy for GCA. 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 (250–1,000 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 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 patients from sleep [42]. 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 disease, renal disease, gastrointestinal disease, and metabolic bone disease. Patients may also have peripheral joint involvement (large joints are more commonly involved than small joints). Patients may also complain of other sites of enthesopathic pain (e.g., Achilles tendon, plantar fascia). 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 [43].

Early diagnosis of AS is important to maximize functional outcomes. The diagnosis of AS is based on a combination of clinical and radiographic findings [44, 45], Table 5. The insidious onset of low back pain

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Table 5 New York and Rome criteria for diagnosis of ankylosing spondylitis

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

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 [46].

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 [47], but the cardiopulmonary, renal, gastrointestinal, and neurovascular systems can all be involved.

Radiographic studies help to confirm the diagnosis of AS [48]. 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. 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 unresponsive to NSAIDS. TNF-α antagonists are effective in the treatment of AS [49]. Infliximab, adalimumab, golimumab, certilizumab pegol, and etanercept have all been approved by the FDA as therapy for AS when NSAID therapy has 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 [50], and orthopedic surgery depending on the extent of disease.

Psoriatic Arthritis

Psoriatic arthritis is a seronegative inflammatory arthritis that is variable and ranges from 7 % to 42 % in studies (chapter "► Psoriatic arthritis is a seronegative inflammatory arthritis"). Psoriasis typically precedes the appearance of arthritis by several years. The onset is typically insidious with patients primarily

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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 [51] include the Classification Criteria for Psoriatic Arthritis (CAPSAR) 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 shoe the characteristic "pencil-in-cup" deformity. NSAIDs are the initial treatment of choice, and several disease-modifying antirheumatic drugs have been approved for the treatment of psoriatic arthritis including methotrexate, sulfasalazine, cyclosporine, leflunomide, and TNF-α antagonists [52]. Recently, apremalist (a phosphodiesterase-4 inhibitor) has been approved by the FDA for treatment of psoriatic arthritis in adults [53].

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Selected Disorders of the Musculoskeletal System

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Problems of the Soft Tissues

Fibromyalgia

Definition/Background

Fibromyalgia is a common syndrome characterized by generalized pain present for greater than 3 months, joint stiffness, fatigue, mood disorders, cognitive dysfunction, nonrestorative sleep, and tender points.

First described in the ninth century in Germany, fibromyalgia continues to remain a poorly understood condition that is difficult to diagnose and manage. In early 1900s, the term fibrositis was used to describe the condition since it was thought that inflammation of the connective tissue caused it. However, further systematic scientific studies in the mid-1970s revealed that inflammation was not the contributing factor and the term "fibromyalgia" was coined as a pain syndrome without any specific organ disease [1]. In 1980, a multicenter study was conducted, and two criteria emerged, commonly referred as the American College of Rheumatology (ACR) criteria, for diagnosing fibromyalgia [2]. The first is a history of widespread pain of 3 months or longer duration, and the second is the presence of pain responses at least 11 of 18 designated tender points (TP) (Fig. 1). A newer ACR criterion was formulated in 2010; this criterion is described later in this chapter.

Epidemiology

Fibromyalgia is the third most common rheumatic disorder after osteoarthritis and back pain. The prevalence has been estimated to range from 2 % to 8 % of the population in North America [3]. In 2005, it was estimated that 5 million adults were suffering from fibromyalgia. It is more prevalent in females than in males; using the 1990 ACR criteria, the female–male ratio was 7:1, but the newer ACR diagnostic criteria from 2010 put the ratio at 2:1, similar to other chronic pain conditions.

While it can develop at any age, including childhood, prevalence usually increases with age, with symptoms commonly presenting between 35 and 60 years of age. Genetic predisposition is likely, evidenced by the increased prevalence of fibromyalgia and chronic pain conditions, in family members of fibromyalgia patients. Environmental factors, certain infections, and psychosocial stressors have also been implicated as being likely triggers of risk factors for fibromyalgia. These factors include trauma, poor sleep, obesity, physical inactivity, viral infections, Q fever, Lyme disease, poor job/life satisfaction, or deployments to a war zone.

Other chronic pain conditions are also commonly associated with fibromyalgia. These include but are not limited to headaches, chronic fatigue, restless leg syndrome, irritable bowel syndrome, interstitial cystitis, dysmenorrhea, endometriosis, temporomandibular joint disorder, rheumatoid arthritis, and low back pain [4].

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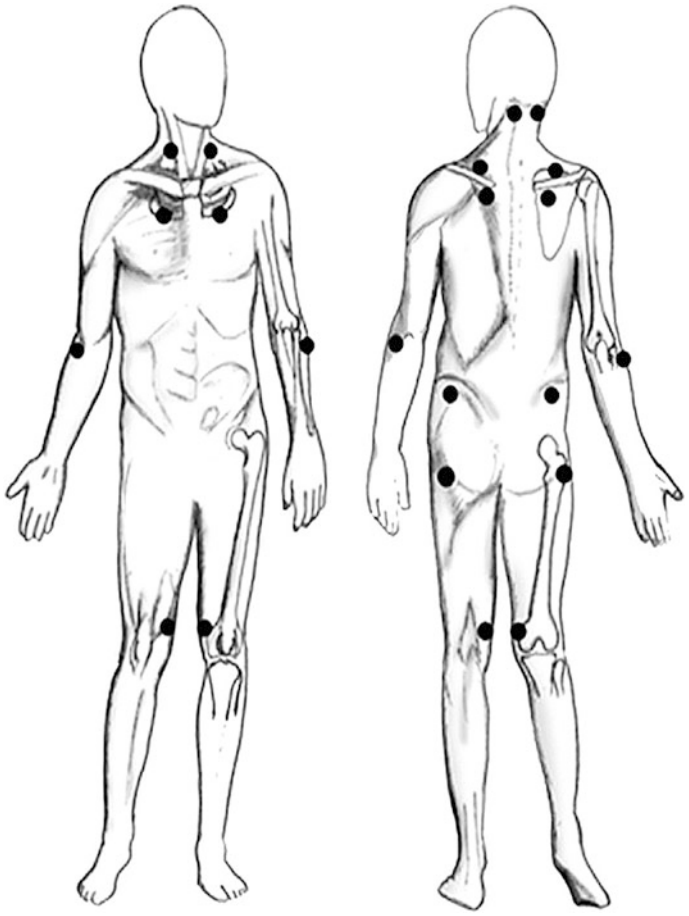

Fig. 1 Tender points location in fibromyalgia (Adapted from Pain Res Treat. 2012; 2012: 426130. © 2012 Enrico Bellato et al., open access article distributed under the Creative Commons Attribution License)

The economic burden of this condition is also significant both on the individual patient as well as the society in general. It has been estimated to be, on average, $35,000 per patient per year, which accounts for both direct costs and indirect expenses. The costs have been estimated to be, on average, medications, treatment costs, and rehabilitation expenses; indirect costs include lost wages, disability, and lost productivity resulting from absenteeism and presenteeism.

Etiopathogenesis

Though fibromyalgia was originally thought to be an inflammatory condition (fibrositis), this has been refuted with later studies. While the exact etiology is still unknown, the general consensus over the past few decades has been that several factors contribute to this process with central sensitization being considered as one of the primary mechanisms. Central sensitization is described as the increased response to stimulation as a consequence of spontaneous nerve activity, enlarged receptive fields, and augmented stimulus responses transmitted by afferent fibers [5].

Other mechanisms include hypothalamic-pituitary-adrenal (HPA) axis dysfunction, sleep disruptions, genetic factors, neurotransmitter imbalances, peripheral pain modulations, psychiatric conditions, and trigger factors. While multiple mechanisms have been attributed, it is important to note that a majority of the patients might not have any precipitating factors.

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Clinical Features

Widespread pain and tenderness remain the hallmark of fibromyalgia. The pain is often described as diffuse, multifocal, deep, gnawing, and burning. It is frequently migratory and often waxes and wanes. Other systemic symptoms such as fatigue and disruptive sleep patterns are quite common. Nonspecific symptoms such as chronic headaches, tingling and numbness, stiffness – especially in the mornings – weight fluctuations, heat and cold intolerance, restless legs, and paresthesias are also reported. Decline in cognitive functions and mood disturbances such as depression and anxiety can also occur at a higher rate in patients with fibromyalgia than the general population. The symptoms appear to worsen with changes in weather, stressful situations, during menstrual cycles, and physical exertion.

Diagnosis

The diagnosis is predominantly made from eliciting the typical history of generalized pain over three months and presence of tender points on physical examination.

In 1990, the ACR criteria were published as a standard for diagnosing fibromyalgia for research proposes, but since then, it has been widely used to clinically diagnose the condition. The pain must affect both sides of the body; it must affect areas above and below the waist; and it must be axial. Tender points are considered positive if pain is elicited with digital palpation with about 4 kg (8.8 lb) of pressure (thumbnail bed blanches). There should be at least 11 of the 18 specified tender points shown in Fig. 1.

Although being widely accepted as the standard for diagnosis, there were many shortcomings in these criteria. Most notably among them was that the primary care provider rarely performed tender point examination even though it was diagnosed most commonly in the primary care setting. The importance of symptoms, based on which the diagnosis was made, was not considered in the 1990 ACR criteria.

In 2010, ACR developed a new diagnostic criteria which include widespread pain index (WPI) and symptom severity scale (SS) [6] (Table 1). The new case definition and diagnostic criteria for fibromyalgia (which includes WPI $\geq$7 and SS $\geq$5 or WPI3-6 and SS $\geq$9) capture 88 % of cases classified by the ACR 1990 classification criteria and do not require a physical or tender point examination.

Basic laboratory tests including complete blood count, erythrocyte sedimentation rate, C- reactive protein, thyroid panel, vitamin D levels, and routine serum chemistries are done primarily to rule out the differentials rather than to rule in fibromyalgia.

Differential Diagnosis

The differential diagnosis for fibromyalgia includes hypothyroidism, rheumatoid arthritis, adrenal dysfunction, systemic infections, and mental health disorders.

Treatment

The goal of treatment should be a multidisciplinary approach to alleviate pain, improve sleep and functioning, and reduce associated symptoms (Fig. 2).

Patient Education. Patient education is essential in aiding understanding, acceptance, and self-management of the condition. There is evidence that educational sessions to explain the condition and set treatment expectations are effective [7]. Various resources such as the Fibromyalgia Impact Questionnaire (FIQ; www.myalgia.com), Patient Global Impression of Change (PGIC), and support groups online and in person are useful tools.

Pharmacological Therapies. The US Food and Drug Administration (FDA) has approved the following medications for fibromyalgia:

Pregabalin.This is a gamma-aminobutyric acid (GABA) analog and an antiepileptic agent that has been found to be effective in pain reduction and improvement in sleep and quality of life measures. The

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Table 1 ACR 2010 fibromyalgia diagnostic criteria (Reprinted with permission from Arthritis Care and Research, 62 (5) May 2010, pp 600–610)

Criteria			
A patient satisfies diagnostic criteria for fibromyalgia if the following three conditions are met:			
1) Widespread pain index (WPI) ≥7 and symptom severity (SS) scale score ≥5 or WPI 3-6 and SS scale score≥9			
2) Symptoms have been present at a similar level for at least 3 months			
3) The patient does not have a disorder that would otherwise explain the pain			
Ascertainment			
1) WPI: note the number areas in which the patient has had pain over the last week. In how many areas has the patient had pain? Score will be between 0 and 19			
Shoulder girdle left	Hip (buttock trochanter) left	Jaw, left	Upper back
Shoulder girdle right	Hip (buttock trochanter) right	Jaw, right	Lower back
Upper arm, left	Upper leg, left	Chest	Neck
Upper arm, right	Upper leg, right	Abdomen	
Lower arm, left	Lower leg, left		
Lower arm, right	Lower leg, right		
2) SS scale score:			
Fatigue			
Waking unrefreshed			
Cognitive symptoms			
For each of the three symptoms above, indicate the level of severity over the past week using the following scale			
0 = no problem			
1 = slight or mild problems, generally mild or intermittent			
2 = moderate, considerable problems, often present, and/or at a moderate level			
3 = severe, pervasive, continuous, life-disturbing problems			
Considering somatic symptoms in general, indicate whether the patient has[a]			
0 = no symptoms			
1 = few symptoms			
2 = a moderate number of symptoms			
3 = a great deal of symptoms			
The SS scale score is the sum of the severity of the three symptoms (fatigue, waking unrefreshed, cognitive symptoms) plus the extent (severity) of somatic symptoms in general. The final score is between 0 and 12			

[a]Somatic symptoms that might be considered: muscle pain, irritable bowel syndrome, fatigue/tiredness, thinking or remembering problem, muscle weakness, headache, pain/cramps in the abdomen, numbness/tingling, dizziness, insomnia, depression, constipation, pain in the upper abdomen, nausea, nervousness, chest pain, blurred vision, fever, diarrhea, dry mouth, itching, wheezing, Raynaud's phenomenon, hives/welts, ringing in ears, vomiting, heartburn, oral ulcers, loss of/change in taste, seizures, dry eyes, shortness of breath, loss of appetite, rash, sun sensitivity, hearing difficulties, easy bruising, hair loss, frequent urination, painful urination, and bladder spasms

starting dose is 75 mg BID and can be titrated up to 300–450 mg/day. Adverse effects include dizziness, dry mouth, blurred vision, weight gain, somnolence, peripheral edema, and concentration problems.

Serotonin Norepinephrine Reuptake Inhibitors (*SNRIs*). Duloxetine and milnacipran reduce pain by increasing activity of noradrenergic antinociceptive pathway [8]. There is also significant improvement in other subjective ratings of fibromyalgia symptoms (PGIC; FIQ total score).

Duloxetine should be considered in patients presenting with significant depression symptoms. The starting dose is 30 mg/day and can be titrated up to 60 mg/day. Adverse effects include nausea, somnolence, dry mouth, fatigue, constipation, and increased sweating.

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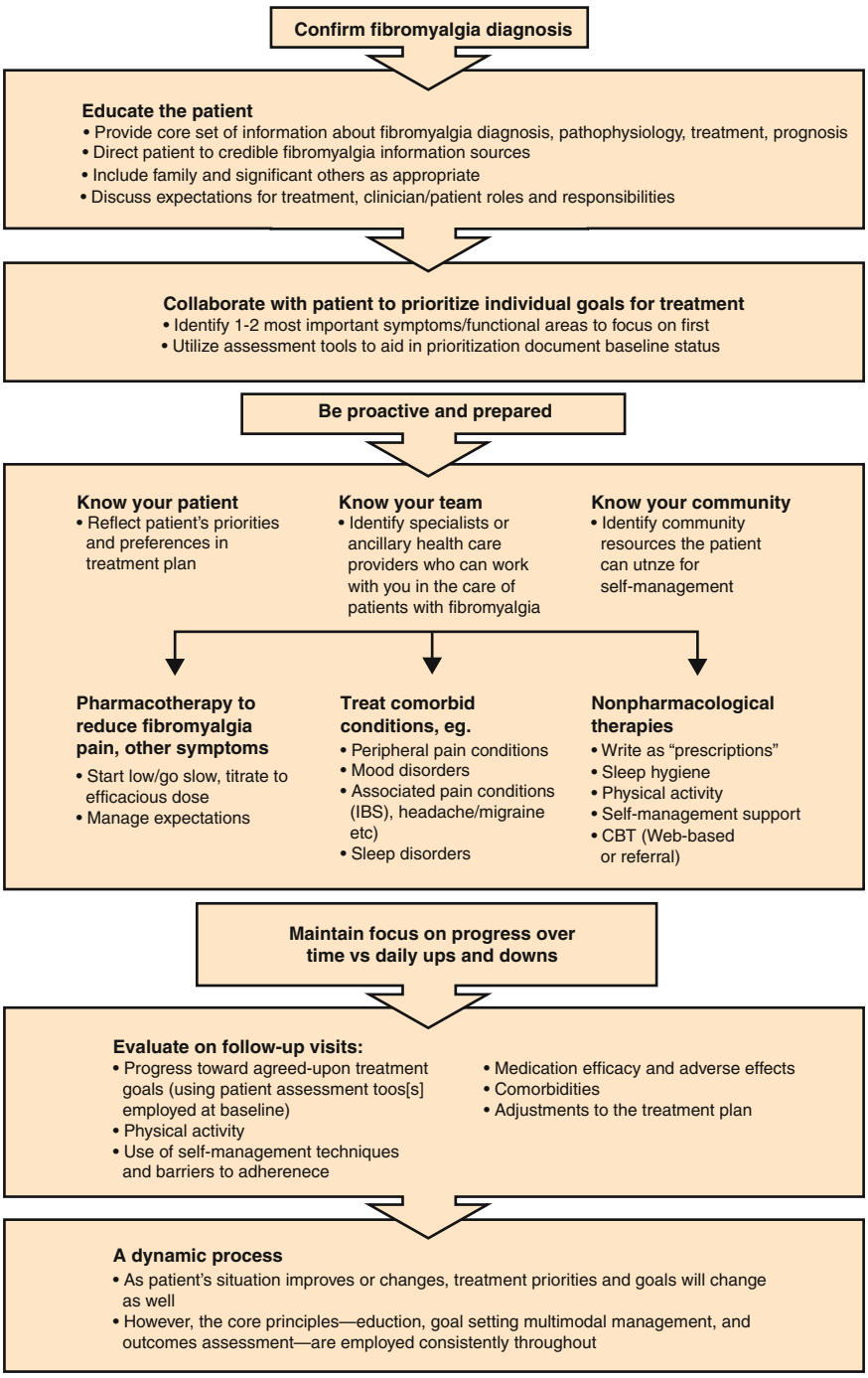

Fig. 2 Multidisciplinary approach for fibromyalgia management (Reprinted from Ref. [43], Copyright (2012), with permission from Elsevier)

Milnacipran is helpful in patients with significant fatigue or cognitive dysfunction. The starting dose is 12.5 mg/day and can be titrated up to 50 mg BID. Adverse effects include nausea, headaches, palpitation, hot flushes, and hypertension.

Other medications, although not approved by FDA, that continue to be used in the management of fibromyalgia include tricyclic antidepressants, specifically amitriptyline and cyclobenzaprine in low doses. Gabapentin, tramadol, fluoxetine, and sodium oxybate are also used for symptomatic relief with

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some efficacy. NSAIDs have not been found to be effective in the management of fibromyalgia but continue to be used in the management.

Exercise/Physical Activity. Aerobic exercise and strength training have been consistently linked to improvement in symptoms. Moderate intensity aerobic training for 12 weeks may improve overall well-being and physical function, but it offers little or no difference in pain or tender points. Strength training for 12 weeks may result in large reductions in pain, tender points and depression, and large improvement in overall well-being but may not lead to any difference in physical function [9].

The most effective recommendation is to start with low impact activity such as walking for 10 min/day and build up to 30–60 min of activity 2–3 times for week.

While various physical activity modalities such as tai chi, yoga, and balneotherapy have been described in the literature, effectiveness is yet to be conclusively demonstrated for management of fibromyalgia.

Cognitive Behavioral Therapy. Cognitive behavioral therapy (CBT), especially pain-based CBT, has been shown to be effective [10]. It is also effective in improving mood, quality of life, and cognitive functioning, especially when included as a part of a multidisciplinary treatment program. CBT can be offered in individual session, small groups, and also online. The Internet-based programs offer more convenience and flexibility to the patients.

Complementary and Alternative Medicine (*CAM*) *Therapies*. Therapies such as acupuncture, hypnotherapy, and mindfulness-based stress reduction (MBSR) are increasingly being used in the management of fibromyalgia, but due to limited number of good quality studies, the clinical benefit of these modalities cannot be determined at the current time.

Myofascial Pain Syndrome

Definition/Background

Myofascial pain syndrome (MPS) is a specific syndrome characterized by a complex of sensory, motor, and autonomic symptoms that are caused by myofascial trigger points [11]. Trigger points are spots of exquisite tenderness and hyperirritability in muscles or their fascia, localized in taut, palpable bands, which mediate a local twitch response of muscle fibers under a specific type of palpation and give rise to pain, tenderness, and autonomic phenomena. This is a common pain condition that is frequently underdiagnosed due to a lack of validated diagnostic criteria and overlap of symptoms with those of other musculoskeletal pain disorders.

Clinical Features

MPS typically presents as a deep somatic pain that is described as constrictive or cramping in nature. It is fairly well discriminated, varies in intensity, and usually prevalent in the head, neck, shoulders, hips, or low back, as these muscles work consistently against gravity or repetitively. Often a history of muscle trauma can be elicited which could be overload, excessive stretching, or overuse. Altered motor functions such as weakness, decreased work tolerance, and loss of coordination are also present. Autonomic disturbances include cooling, sweating, persistent lacrimation, imbalance, dizziness, and tinnitus.

The affected muscles are palpitated to search for the taut bands and to localize the trigger points within the identified band. A *jump sign* is elicited as a pain response when digital pressure is applied on the trigger point resulting in the patient wincing and suddenly moving the limb segment activated by the affected muscle group [12].

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Diagnosis

Diagnosis is predominantly based on clinical findings. There are no established diagnostic laboratory tests or examinations. According to Simon et al., MPS can be diagnosed if five major criteria and at least one minor criterion are satisfied [13].

The major criteria are (1) localized spontaneous pain, (2) spontaneous pain or altered sensation in the target area, (3) taut palpable band in an accessible muscle, (4) exquisite localized tenderness in a precise point along the taut band, and (5) reduced range of motion.

Minor criteria include (1) reproduction of spontaneously perceived pain and altered sensations by pressure on the trigger points, (2) elicitation of a local twitch response, and (3) pain relived by muscle stretching or injection of the trigger point.

Management

Medications such as ibuprofen in combination with sedatives, topical analgesics, and amitriptyline have demonstrated some beneficial effects in clinical studies. Other modalities of treatment include trigger point release, which can be achieved by muscle stretch, and trigger point injections (with anesthetic or dry needling). Trigger point injections are effective in providing prompt relief of symptoms. Injections of botulinum toxin are also used although there is no strong evidence for their clinical effectiveness. Therapeutic ultrasound and laser therapy are other emerging treatment modalities.

Complex Regional Pain Syndrome (CRPS)

Definition/Background

Complex regional pain syndrome is a disabling pain condition with sensory, motor, and autonomic manifestation. Initially termed as Sudeck's dystrophy in 1900, this was considered to be acute inflammatory bone atrophy. As growing evidence revealed an inflammatory as well as sympathetic pathogenesis, it was renamed reflex sympathetic dystrophy. Finally, in 1993, the International Association for the Study of Pain (IASP) introduced the current descriptive term CRPS. It is further subdivided into CRPS I, if there is no obvious nerve injury, or CRPS II, if associated with nerve injury [14]. The pathogenesis, while not conclusive, can be attributed to facilitated neurogenic inflammation, autonomic dysfunction, and neuroplastic changes within the CNS.

Clinical Features

Clinical features include a characteristic triad of autonomic, sensory, and motor disturbances. Distal edema is present in over 80 % of cases and this is worsened by orthostasis and physical strain. Skin temperature changes and trophic changes of the skin, hair, and nail are also noticed. In prolonged cases, atrophy of the skin and muscle is also evident. Burning or stinging pain is commonly reported and this is worsened by anxiety, temperature changes, and orthostasis at night. Glove and stocking distribution of sensory changes, mainly hyperalgesia, is also present. Motor weakness is also reported in a majority of patients.

Diagnosis

Diagnosis is made based primarily on clinical history, examination, and exclusion of other causes. There are various diagnostic criteria established such as IASP criteria, Budapest criteria, and Veldman criteria [15]. Objective testing such as thermography, Doppler, x-ray, and bone scans can be helpful in certain situations. The differential diagnoses include rheumatic disease, inflammatory conditions, compartment syndromes, and nerve injury syndromes.

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Management

Management includes both pharmacotherapeutics and nonpharmacological therapies.

Glucocorticoids especially in the initial phase of edema and hyperthermia have demonstrated positive effects. The dose recommended is prednisone 100 mg/day titrated down by 25 mg every 4 days.

Bisphosphonates were found to be effective in decreasing pain when compared with placebo in patients with bone abnormalities. The medications studied were IV pamidronate (60 mg, intravenous) and alendronate (40 mg PO daily for 8 weeks).

Ketamines intravenously in low doses have moderate evidence for effectiveness in longstanding CRPS.

Physiotherapy and occupational therapy in conjunction with a variety of interventional pain management techniques (discussed below) are described as evidence-based guidelines for management of CRPS I. Activities such as active range of motion, water-based exercises, stress loading, sensorimotor treatment, education, graded exposure to activities, and mirror box therapy have been found to be effective.

Interventional pain management approaches include stellate ganglion blockade, lumbar sympathetic blockade, spinal cord stimulation, and repetitive transcranial magnetic stimulation (rTMS).

Prognosis

Every patient should be treated early and aggressively in the hope of preventing chronicity. In a substantial number of patients, resolution occurs spontaneously, while in others, it may cause ongoing intense pain.

Neuroma

Neuroma is a benign mass that occurs secondary to nerve irritation or injury. Following a partial or complete injury, the nerve tries to establish continuity with its distal end, resulting in a proliferation of disorganized axons, myofibroblasts, endothelial cells, and Schwann cells, leading to a neuroma [16]. Neuromas can present with disabling pain or loss of motor functions. A history of sharp trauma, crush, or stretch injury is often present along with pain related to a single peripheral nerve distribution with or without accompanying numbness or diminished sensation. Tinel's sign (sensation of tingling when an injured nerve is stimulated via light percussion) indicates regeneration of axons and can be elicited from a terminal neuroma. Other diagnostic measures including anesthetic injection and imaging procedures such as ultrasound and MRI may be useful.

In the upper extremity, the most common locations for a neuroma are in the thumb (bowler's thumb). This a pathologic condition associated with bowlers because of the impingement of the bowling ball on the thumb, resulting in repeated minor trauma to the ulnar digital nerve of the thumb. In the lower extremity, Morton's neuroma is the most common type. It is a painful neuropathy resulting from compression of the plantar interdigital nerve between the metatarsal heads and is a common cause of forefoot pain.

Oral analgesics may have some efficacy in the medical management of neuropathic pain. Antidepressants, anticonvulsants, and opioids are used, but their effectiveness is not well studied [17]. When conservative methods fail, operative techniques include resection of the neuroma, use of nerve grafts to reconnect the severed proximal and distal stumps, containment of the neuroma, and translocation of the nerve. A majority of the patients respond favorably to surgery.

Dupuytren's Contracture

Dupuytren's contracture is a benign connective tissue disorder affecting the palmar fascia, which leads to progressive hand contractures resulting in restricting a person's ability to undertake daily activities. This deterioration in hand function is the main reason for seeking treatment. This is most commonly seen in older men of northern European descent (e.g., Celtic, Scandinavian) and is a disorder of autosomal

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dominant inheritance. It is commonly seen in association with diabetes, HIV, epilepsy, alcoholism, and cigarette use [18].

Clinical Features

These features include nodule formation near the MCP joint on the palm of the hand or skin pitting and thickening at that site. The advanced stage may present with cord formation, with the ring and small finger being affected first and gradually progressing to the other fingers. A positive (or failed) tabletop test has been shown to correlate with a MCP joint contracture of 40°. Here the patient is unable to lay his palm and fingers simultaneously flat on a hard surface. This is often used as a screening test for Dupuytren's contracture.

Treatment

Operative intervention remains the gold standard for treatment in cases of advanced disease with contractures. Procedures include needle aponeurotomy, open or percutaneous fasciotomy, and open fasciectomy [19]. Numerous nonoperative modalities, including splinting, physical therapy, and corticosteroid injections, have not been found to be beneficial with regard to long-term outcome.

Collagenase clostridium histolyticm is a minimally invasive, nonsurgical option that has recently been approved by the US FDA. Collagenase is injected directly into Dupuytren's cord leading to lysis of the collagen followed by joint manipulation in an attempt to rupture the cord. Both the injection and subsequent cord rupture can be safely conducted in a medical office. Long-term results and recurrence rates of this procedure are currently being studied.

Ganglion Cysts

This is the most common soft tissue swelling in the hand and wrist. These are benign cysts that are found near a joint capsule, tendon, or tendon sheath. They are more common in women and typically present between the third to sixth decades of life. They can develop suddenly or gradually and can resolve spontaneously in almost half of the cases. While they are usually painless, pain can sometimes be the presenting symptom, especially when the cyst is exerting pressure on a nerve or underlying structure. On palpation, they are typically smooth, mildly tender masses, and may be single or multilobular. Transillumination helps to differentiate between solid and cystic masses. Advanced imaging such as magnetic resonance imaging or ultrasonography is sometimes needed for diagnosis. Treatment includes reassurance, aspiration, and excision [20]. As a majority of the ganglion cysts are asymptomatic, small, and often resolve spontaneously, reassurance that these are not malignant is often sufficient. Aspiration alone is one of the simplest ways to treat ganglion cyst and can be done in the office setting. Caution needs to be exercised when aspirating volar wrist ganglion cyst due to the close proximity of the radial artery. Aspiration is associated with a high recurrence rate. Other conservative methods of management include steroid or hyaluronidase injections, sclerotherapy, and immobilization, but these are not widely adopted. Surgical excision remains the most effective treatment of symptomatic ganglion cysts with a low recurrence rate of 1–4 %.

Abnormalities of Bone

Benign Tumors

There are multiple types of benign bone tumors: bone forming, cartilage forming, and fibrous tumors. These tumors do not metastasize. Important factors in the diagnosis of a bone tumor includes patient's age and gender, the bone involved, location of the tumor on the bone, lesion margin, and periosteal reaction

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Table 2 Skeletal abnormalities by age and common presentation site

Skeletal abnormality	Age at peak incidence	Common locations
Benign tumors		
Osteochondroma	10–30	Metaphysis of long bones
Osteoma	Any	Skull
Osteoid osteoma	5–25	Long bones, spine
Chondroma	20–50	Hands, metaphysis of long bones
Giant cell tumor	20–45	Epiphysis and metaphysis of long bones
Malignant tumors		
Ewing's sarcoma	5–30	Marrow sites (vertebrae, ribs, sternum, pelvis) and proximal long bones at the diaphysis (femur, humerus)
Osteosarcoma	10–40, 60+	Proximal long bones metaphysis (humerus, femur) and pelvis
Primary chondrosarcoma	50–80	Pelvis, hips, shoulder, skull, facial bones
Chordoma	30–80	Base of skull or sacrum
Metastatic malignant tumors	40+	
Non-ossifying fibroma	10–20	80 % occur metadiaphysis of tibia and diatal femur
Paget's disease of bone	50–90	Skull, spine, pelvis, lower appendicular skeleton

(Table 2) [20]. As comprehensive inclusion of all types of tumors is beyond the scope of this chapter, some of the most common benign bone tumors are discussed here.

Osteochondroma

Osteochondroma, also known as exostosis, is a relatively common developmental lesion that forms when fragments of the epiphyseal growth plate or cartilage herniate through the periosteal covering of bones [21]. It is composed of lamellar bones covered by a cartilage cap. The cartilage cap is covered by perichondrium and usually less than 2 cm in thickness. While most of the osteochondromas occur spontaneously, cases following prolonged radiation treatments have also been described. The metaphysis of long bones are the preferred site, but it can arise in flat bones like the ilium and scapula and also in the spine, with cervical spine being the most common location. There is a male preponderance, and majority of the patients are younger than 20 years of age. Painless swelling and cosmetic deformity are the most common presenting symptoms.

Osteoma

This asymptomatic, slow growing tumor is usually an incidental finding. It is most commonly found in the skull and occasionally in the long bones. Osteomas may occur at any age and on rare instances can cause obstructive symptoms especially in the sinuses resulting in headaches and sinusitis. On imaging, they appear as a sharply defined bony surface lesion arising from the cortex [22]. Multiple osteomas are associated with Gardner syndrome and tuberous sclerosis.

Osteoid Osteoma

Osteoid osteoma is a benign lesion of the young and that is two to three times more likely to occur in males than females. It often presents as joint pain, worse at night, and may have an associated effusion. It is the most common cause of painful scoliosis in children. Symptomatic presentation may be difficult to

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distinguish from stress fractures or osteomyelitis. On plain films, cortical thinning and sclerosis are often present in the affected long bones. These lesions are often sensitive to nonsteroidal anti-inflammatory medications. More definitive treatment has been achieved with surgical excision and more recently radiofrequency ablation. Osteoid osteomas greater than 2 cm are pathologically identified as osteoblastomas [20, 22].

Chondroma

Chondromas are benign cartilaginous tumors subdivided by the area of bone affected, those in the medullary region labeled as enchondroma and those more superficial as periosteal chondromas. They are often found incidentally in asymptomatic patients between the ages of 20–50. Areas commonly involved include the hands and long bones. When patients present with pain or atypical radiographic findings, the diagnosis of low-grade chondrosarcoma must be excluded. Surgical excision is often unneeded unless patients are symptomatic. Younger patients who have several chondromas may present with bony abnormalities or pathologic fractures as part of Ollier's disease and Maffucci's syndrome. These patients are also at increased risk of developing chondrosarcomas [20, 22, 23].

Giant Cell Tumor

Giant cell tumors are a benign rare form of aggressive lesions that affect the epiphyseal long bones of adults 20–45 years old. Symptoms often present as pain, tenderness, swelling, and limitations of joint motion. Left untreated significant localized destruction and joint immobility occur. Plain films are often characterized with an enlarging radiolucent lytic lesion with minimal sclerosis. These lesions can extend into the metaphysis and surrounding soft tissues. Systemic metastasis is very rare; however, secondary lesions of the lung have been recorded. Patients treated solely with surgical excision have an 18–50 % rate of relapse, with reoccurrence within 2 years [20, 22, 24].

Malignant Tumors

As a subset, malignant skeletal tumors are uncommon. They usually occur in patients under 30 years of age, affecting bones with the highest rate of growth with the distal femur and proximal humerus most commonly affected. These lesions often have aggressive clinical patterns and may spread systemically. Patient age and tumor location often relate to the likely type of skeletal malignancy (Table 2) [25, 26]. The goal of treatment of most primary malignant bone tumors is a negative surgical margin via resection. This treatment often causes a large boney defect that requires reconstruction. Most often, however, it is the deficiencies in the soft tissue that create the major obstacles to limb salvage [25, 27].

Evaluation and diagnosis of any skeletal abnormality begins with plain radiography followed by MRI and/or CT. For lesions in the extremities, images must include the entire long bone as well as the adjacent joints. Biopsies will be required to conclusively determine diagnosis and direct subsequent therapies. Referral to the necessary specialists is therefore required for diagnosis and treatment [26].

Ewing's Sarcoma

Epidemiology Ewing's sarcoma (EWS) and osteosarcoma (OS) are the most common malignant bone tumors of childhood accounting for 6 % of pediatric malignancies. The skeletal variant of EWS is most likely to occur in younger patients and has been more commonly found in Caucasians and males [27, 28].

Clinical Features EWS may present with nonspecific symptoms such as pain, swelling, and palpable mass. In the case of advanced disease and marrow involvement, systemic symptoms such as fever, anemia, and weight loss may occur. This diagnosis may be mistaken for osteomyelitis especially in the

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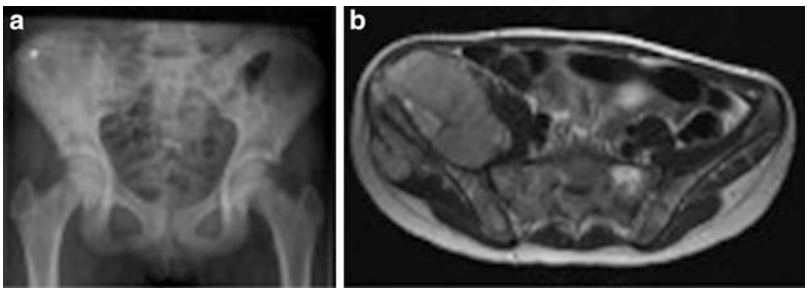

Fig. 3 Ewing's sarcoma. (**a**) AP radiograph of an 11-year-old child shows a destructive lesion of the right iliac bone (*asterisk*) with a permeative and moth-eaten appearance with no obvious soft tissue mass. (**b**) Axial T2-weighted MRI image shows that the radiographic abnormality was associated with a heterogeneous signal intensity large soft tissue mass, which extended anterior and posterior to the right iliac bone. Extensive metastatic disease was also seen within the sacrum and the spine (Reprinted from Clinical Radiology, 68/11, N. Jain, M. Sah, J. Chakraverty, A. Evans, S. Kamath, Radiological approach to a child with hip pain, 1167–1178, 2013, with permission from Elsevier)

setting of systemic symptoms [26]. Appearance of the lesion on x-ray is often described as "moth-eaten" with an "onion peel" appearance of the periosteum (Fig. 3).

Treatment/Prognosis Care often begins with chemotherapy and wide resection when possible. The presentation of tumors in the axial skeleton often affects the ability to achieve wide margins without substantial morbidity. In these cases, adjuvant radiotherapy may be used as EWS is highly sensitive to radiation with a 5-year localized control rate of 53–86 % when radiotherapy is used without surgical intervention [26, 29].

Osteosarcoma

Epidemiology Osteosarcoma affects all age groups and is the most common primary bone tumor [25, 26]. OS and EWS both reach their highest incidence rate during adolescence; however, OS is rarely seen in the very young and has been noted to have a secondary increased incidence in patients 60 years and older [26, 30]. OS is most often seen in males, young blacks, and older white patients. Development of a secondary OS has been primarily linked to prior radiation exposure and/or chemotherapy with anthracycline [26, 27, 31]. OS has also been linked to several cancer-related syndromes such as Werner syndrome, Li-Fraumeni syndrome, and hereditary retinoblastoma [26].

Clinical Features OS often presents with localized pain and swelling, which may be cyclical in nature, and may be accompanied by a tender palpable mass. Systemic complaints are not common and the nonspecific presentation may be mistaken for activity-induced injuries [26]. Laboratory evaluation may reveal elevated alkaline phosphatase, erythrocyte sedimentation rate, and lactate dehydrogenase [32, 33]. Radiographic evaluation of the affected site may present with a mixture of radiodense and lucent areas and a lifting of the cortex forming Codman's triangle (Fig. 4).

Treatment/Prognosis The outcomes of osteosarcoma are most often dependent on the location and grade of the disease, with lesions in the axial skeleton and higher levels of lactate dehydrogenase often indicating worse outcomes. Currently treatment consists of resection and chemotherapy with radiation therapy recommended as an adjuvant treatment [26, 33]. Factors affecting the presence of metastases at diagnosis include older age, involvement of the axial skeleton, greater tumor size, and lower

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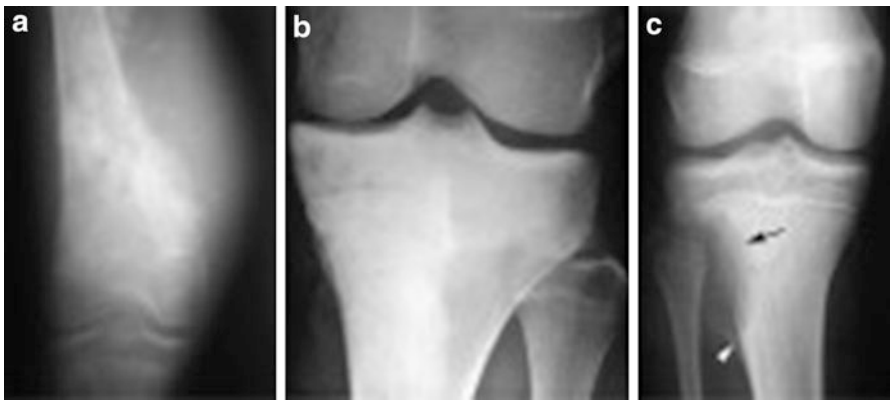

Fig. 4 Osteosarcoma. The varied radiographic appearances of conventional central OS. (**a**) AP radiograph of the distal femur showing a permeative, lytic, and sclerotic lesion with a large soft tissue mass containing immature bone matrix. (**b**) AP radiograph of the proximal tibia showing a predominantly osteoblastic OS, appearing as an area of poorly defined medullary sclerosis with subtle periosteal reaction. (**c**) AP radiograph of the proximal tibia showing a lytic OS (*black arrow*) with a Codman's triangle (*white arrowhead*) demarcating the distal extent of extraosseous tumor (Reprinted from Clinical Radiology, 62/4, Suresh S, Saifuddin A, Radiological appearances of appendicular osteosarcoma: a comprehensive pictorial review, 314–23, 2007, with permission from Elsevier)

socioeconomic status [34]. The 5-year survival rates for osteosarcoma varies drastically by age at presentation with elderly adults having worse prognosis of 24 % versus 62 % [30].

Primary Chondrosarcoma

Chondrosarcomas are rare, slow growing tumors that originate from cartilaginous cells. They occur most commonly between the ages of 20–60. Due to slow progression, prognosis is usually favorable and patients often present with a mass that has been present for years [35]. Patients may complain of pain and tenderness at the site without a palpable mass. Plain films often reveal a defined lytic lesion with associated endosteal scalloping [36]. Treatment of low-grade (Grade-1) cartilaginous lesions includes wide resection, intralesional resection, or curettage and cryosurgery. In patients with more advanced disease, the negative margin resection ± radiation is the treatment of choice. Histopathological stage at the time of diagnosis is the best indicator of outcome in patients with chondrosarcoma, with higher stage linked to worse prognosis. Tumor site has also been associated with worse outcome in patients with pelvic lesions as opposed to those with disease in the extremities [25, 27].

Chordoma

Chordomas are rare tumors affecting the axial skeleton and arise from residuals of the notochord [37]. They are most often located in the sacrum and followed by the base of the skull. Clinical presentation is usually nonspecific and is often diagnosed as pain from disk or other nonspecific musculoskeletal pathologies [38]. The course is often indolent with subsequent metastasis in late disease. Surgery is often the treatment of choice with a high rate of reoccurrence at the treatment site. Recent research has supported the use of high-dose radiation therapy especially for lesions at the base of the skull; however, this method of treatment continues to be controversial [25, 27, 37].

Metastatic Malignant Tumors

Metastasis to the axial skeleton is common in breast, prostate, thyroid, kidney, and lung cancers. Patients may present with pain, hypercalcemia, pathologic fractures, and spinal compression syndromes. Plain radiographs may show lytic or sclerotic lesions. Bone scintigraphy is considered the best method for the

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detection and monitoring of skeletal metastasis. Conclusive determination of tumor origin is determined via biopsy. Treatment of metastatic disease is often specific to the primary disease [39, 40].

Non-ossifying Fibroma

Non-ossifying fibroma (NF), also known as a fibrous cortical defect, is a benign lesion most common in the metaphyseal long bones of children and adolescents. They are often found incidentally as up to one third of healthy children have one or more of these cortical defects. Most NFs are asymptomatic; however, large lesions may cause pain and pathologic fractures. On plain radiograph, the lesion appears ovoid and multiloculated with thinning and expansion of the cortex. Treatment usually consists of observation, especially of asymptomatic lesions, as most resolve without intervention [41].

Paget's Disease of Bone

Epidemiology Paget's disease of bone, also known as osteitis deformans, is a disease of the elderly defined by an excessive breakdown and remodeling of the osseous matrix leading to progressive bony abnormalities. Genetic components and possible links to the paramyxoviruses, canine distemper virus, and respiratory syncytial virus have been identified [42].

Clinical Features Many patients are asymptomatic; however, those with progressive disease may complain of pain. The sequelae of Paget's disease are related to tumor location causing bowing bone deformities, pathologic fractures, osteoarthritis, deafness, headaches, neurologic deficits, and the development of malignant sarcomas. Laboratory analysis reveals elevated levels of alkaline phosphatase, with normal levels of calcium and phosphate. Bone scintigraphy is performed to determine the extent of the disease. On plain radiographs, lytic lesions are often seen in the early phase of the disease (Fig. 5) [42].

Treatment/Prognosis Symptomatic treatment often involves the use of nonsteroidal anti-inflammatory drugs, analgesics, and calcitonin. More targeted therapies may include use of highly potent bisphosphonate drugs shown to improve the extent of osteolytic lesions [42].

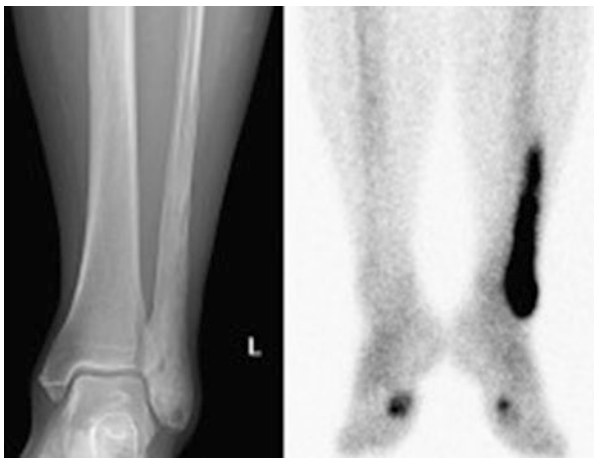

Fig. 5 Paget's Disease. Significant expansion and sclerosis of the distal left fibula with obliteration of the medullary cavity (*left*) is evident on this anteroposterior radiograph. A corresponding solitary region of homogeneous markedly increased uptake is seen on isotope bone scintigraphy (*right*) (Reprinted from Clinical Radiology, 66/7, Cortis K, Micallef K, Mizzi A, Imaging Paget's disease of bone –from head to toe, 662–72, 2011, with permission from Elsevier)

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Family Medicine
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Common Dermatoses

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General Principles

Dermatologic conditions are very common and will affect most individuals at some point in their lifetime, accounting for many family physician office visits. Acute conditions may require treatment or can be self-limited. Others are chronic needing daily treatment or recurring in episodes. Some conditions may require assistance of a dermatologist for immunosuppressive treatment to prevent complications such as conditions seen in patients with psoriatic arthritis.

Patients presenting history, age, length of time of condition, previous episodes, and family history can be useful in diagnosing recurring immune conditions. Records of previous treatments attempted by the patient whether they were helpful or not are also useful in managing skin conditions. Chronic skin conditions can be disruptive to the well-being such as the sleep problems associated with itching all night in atopic dermatitis. Disfiguring conditions, extensive psoriasis, and hidradenitis can result in isolation and depression, and the physician should be mindful of these comorbidities.

Physical Exam

Elements of the physical exam should include a good description of the lesion located in the epidermis or dermis, parts of the body affected (i.e., only sun-exposed areas or areas reachable by scratching), and areas of perspiration. Ideally, getting a good idea of the type of lesion, scale or plaque, bulla, vesicle, papules, and nodules, can help determine the diagnosis. Wood's lamp can assist in the diagnosis of fungal elements.

Laboratory

KOH prep can be helpful in either confirming the presence of fungal elements or eliminating the possibility of a tinea infection. Blood tests can assist in cases where the skin condition may be reflective of a rheumatologic illness or infection. The physician should consider ordering labs such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rapid plasma reagin (RPR) and B12, and vitamin C for possible nutritional deficiencies, inflammatory conditions, or syphilis. Biopsy can be used to confirm a diagnosis when attempted treatment has not been fruitful or to rule out dysplastic lesions.

Chronic Recurring Dermatitis

Atopic Dermatitis aka Eczema

General Principles

Definition Atopic dermatitis (AD) is a chronic skin condition characterized by recurrent pruritus and inflammation. It is now known to be due to a mutation on the FLG gene [1], which encodes for pro-filaggrin, a precursor of filaggrin, the substance that forms the natural skin barrier of the epidermis.

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This results in the dysfunction of epidermal hydration and immune reactions. Additionally, patients with AD have exaggerated inflammatory responses to minor skin irritations and skin infections.

Epidemiology AD may affect as much as one in four children and 2–3 % of adults [1]. It is more common in families with a history of atopy, African-American race, and those living in urban areas. Diet modifications do not appear to decrease the risk of developing AD; cat ownership appears to increase the risk although dog ownership is protective.

Classification No specific classification exists, but there are several variants.

Nummular eczema – lesions in papules or around plaques.

Dyshidrotic eczema (pompholyx) – a variant of hand eczema with scaling of hands and small vesicles between fingers [2].

Approach the Patient

It is important to consider how symptoms are affecting the patient. Over 50 % of children have severe itching that is correlated with decreased quality-of-life ratings [1]. Poor sleep impacts on daily activity, potentially school progress, and can affect the family. In addition, pediatric compliance can be variable as daily treatments can be tedious and some parents may just assume their child is doing it. When performing follow-up, care should be taken to determine if the types of medications are tolerable to the patient, for example, some ointments may be so uncomfortable/greasy that these pts may do better with creams. Cost consideration/insurance coverage is important in selecting treatment, as some of the newer agents are expensive.

Diagnosis

Criteria required for a diagnosis include pruritus and chronic or recurrent eczematous skin findings [1].

History Patients will complain of recurrent itchy dry patches, which tend to improve with treatment and then relapse. Pruritus can be severe, disrupting sleep and the quality of life, and worsen during seasons with low humidity. Supporting history includes early age of onset, atopy in patient or family members, immunoglobulin E reactivity, and dry skin. There are several associated conditions the family practitioner may also be treating such as rhinitis, asthma, food allergies, and depression. Family history often includes allergies, allergic rhinitis, and asthma.

Physical Exam The skin can have different appearances, but typically patients will have dry skin with patches of thickened skin with erythema and edema. Vesicles and papules may be present. Excoriations can lead to lichenification. Secondary infections can appear as oozing over crusty skin patches. There are findings that are more common in AD patients: keratosis pilaris, pityriasis alba, cheilitis, dry skin, follicular enlargement, and hyperlinearity. AD typically is located on the face in infants, extensor areas in children, and flexural involvement in both adults and kids. Groin and axillary regions are usually spared.

Laboratory Tests Laboratory tests are not typically indicated; however, a KOH test might be helpful in ruling out fungal infection. Total or allergen-specific serum IGE may be elevated but is not present in all patients or routinely tested.

Special Testing Punch biopsy is rarely needed but may be used when the diagnosis is uncertain.

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Differential Diagnosis Seborrheic dermatitis (especially in infants), scabies, contact dermatitis, ichthyosis, cutaneous T-cell lymphoma, psoriasis, neurodermatitis, tinea.

Treatment

Behavioral The mainstay of treatment includes daily moisturizers and avoidance of itching. Moisturizers should be applied soon after bathing. Emollients are agents that lubricate and occlude the skin to form a barrier layer; liberal and frequent reapplication should be done to avoid dry skin. Patients should be given a choice in the type of vehicle of moisturizer to improve compliance. Studies have not consistently shown any clear benefit related to frequency or duration of bathing, but it is recommended that once-daily bathing of 5 min or less can remove crusts and should be followed immediately by application of moisturizer [3].

Patients should be instructed to avoid known allergens. Cleansers should be limited to neutral or low pH types, hypoallergenic, and fragrance free. Regular soaps are not recommended.

Medications Treatments typically consist of topical steroid creams and/or calcineurin inhibitors.

Topical steroids (TSs) decrease pruritus and acute and chronic inflammation [3]. Low-potency TS or calcineurin inhibitors (CI) are agents used over thin-skinned sites such as the face, neck, and other skinfolds (see Table 1). Moderate- to high-potency steroids are used over moderate and thick skin. TS should be applied daily during outbreaks or when inflammation is severe for up to several weeks. When outbreaks resolve, TS should be used once to twice weekly for maintenance over sites of recurrent inflammation [3]. Twice-daily application is prescribed most often, but once-daily application of potent steroids is also effective. Systemic absorption is only seen when large amounts of very high-potency steroids are used for extended periods of times or inappropriately in young children. Side effects can include telangiectasias, acneiform eruptions, and skin atrophy. Many of these side effects are reversible [4]. Undertreatment can occur as physicians and patients may be worried about side effects of steroids. Patients may be wary of using steroids due to the knowledge of side effects; they should be reassured that when used correctly, they are effective and unlikely to cause problems. Topical calcineurin inhibitors (CI) decrease inflammation by altering the abnormal cellular response. They are used for moderate to severe disease in areas where high-potency steroids would be contraindicated such as the face and

Table 1 Commonly used steroids

Group I ultrahigh strength – superpotent		
Vehicle	Generic	Brand
C, O, G, So, F, Sh	Clobetasol propionate 0.05 %	Temovate, Cormax
G, L, O	Betamethasone dipropionate 0.05 %	Diprolene
C	Fluocinonide 0.1 %	Vanos
T	Flurandrenolide 4 mcg/m2	Cordran tape
C, O	Halobetasol propionate 0.05 %	Ultravate
O	Diflorasone diacetate 0.5 %	Psorcon
Group II high strength – potent		
Vehicle	Generic	Brand
O	Amcinonide 0.1 %	Cyclocort
L, O	Betamethasone dipropionate 0.05 %	Diprosone
C, O	Desoximetasone 0.25 %	Topicort
G	Desoximetasone 0.05 %	Topicort
C, G, O	Fluocinonide 0.05 %	Lidex
C, O, So	Halcinonide 0.1 %	Halog

(*continued*)

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Table 1 (continued)

Group III medium to high strength – upper midpotency		
Vehicle	Generic	Brand
C, L	Amcinonide 0.1 %	Cyclocort
C, L	Betamethasone Dipropionate 0.05 %	Diprosone
O	Fluticasone propionate 0.005 %	Cutivate
C, O	Triamcinolone acetonide 0.5 %	Kenalog
Group IV midstrength – medium potency		
Vehicle	Generic	Brand
C, F, G, L, O	Desonide 0.05 %	DesOwen
O	Fluocinolone acetonide 0.025 %	Synalar
C, S_o	Fluocinolone acetonide 0.01 %	Synalar
C, L, O	Triamcinolone acetonide 0.025 %	Kenalog
C, L, O	Triamcinolone acetonide 0.1 %	Kenalog
C, L, O	Mometasone furoate 0.1 %	Elocon
Group V lower strength – midpotency		
Vehicle	Generic	Brand
C, L, O	Betamethasone valerate 0.1 %	Luxiq
C	Fluocinolone acetonide 0.025 %	Synalar
C	Fluticasone propionate 0.05 %	Cutivate
C, L, O	Hydrocortisone butyrate 0.1 %	Locoid
Group VI mild strength – low potency		
Vehicle	Generic	Brand
C, O	Alclometasone 0.05 %	Aclovate
C, G, F, L, O	Desonide 0.05 %	Desonate, DesOwen
C, O	Fluocinolone Acetonide 0.025 %	Synalar
C	Fluticasone propionate 0.05 %	Cutivate
Group VII mild strength – least potent		
Vehicle	Generic	Brand
C, L, O	Hydrocortisone acetate 1 %	Cortaid
C, O	Hydrocortisone 2.5 %	Hytone

C cream, *O* ointment, *G* gel, *L* lotion, *Sh* shampoo, *F* foam, *So* solution, *Sp* spray, *T* tape

skinfolds. Tacrolimus (Protopic) 0.03 % ointment bid is approved for age 2 and older, 0.03 % and 0.1 % for age 15 and older. Pimecrolimus (Elidel) 1 % cream is approved for mild to moderate AD; it is applied twice daily for outbreaks or two to three times weekly to sites of recurrent disease. Side effects include burning. There is a black box warning regarding rare cases of malignancy that have been reported, but recent surveillance data of long-term users has not supported this finding [3]. Infected areas may require treatment with antibiotics such as oral cephalexin (Keflex) and topical mupirocin (Bactroban) and/or the use of diluted bleach baths to help decrease colonization of *Staph aureus*.

Referrals Referral to dermatology may be necessary for severe cases.

Patient Education It should revolve around having patients understand that AD is a relapsing condition that will likely require chronic therapy ranging from moisturizers to increases in intensity of treatment during exacerbations and potentially physician visits for complications. Risks of steroids should be

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discussed with patients, and they should be reassured that research has shown that topical steroid is safe when used appropriately.

Seborrheic Dermatitis (SD)

General Principles

Definition SD is a recurrent inflammatory condition characterized by redness and scaling of the skin that surrounds sebaceous glands. It is thought to be caused by colonization of the *Pityrosporum* (*Malassezia*) yeast [2, 5, 6], which thrives in the setting of an altered composition of sebaceous gland secretions. The inflammation then occurs due to an altered immune response.

Epidemiology SD is more common in males and may start at puberty but more commonly after age 20. There is a variant that occurs in infancy, and SD is more common in patients with HIV and Parkinson's disease [6].

Classification Infantile SD is a self-limited variant that resolves by 3–4 months of age. Severe cases may be due to other underlying medical conditions.

Diagnosis

History Patients will typically report flaking and scaling over a time often starting around puberty. The symptoms may improve and worsen due to stress, fatigue, or new medications. Most patients will have mild itching especially in the scalp.

Physical Examination The physician will see greasy scaling plaques or macules over red inflamed skin. Crusting is common and may be white yellow to brown, thin to very thick. The scaling will appear oily as affected areas have a high concentration of sebaceous glands. Common sites are the face typically eyebrows, eyelashes, nasolabial fold, anterior hairline, posterior ears, glabella, and beard. Groin and axilla may be affected.

Laboratory and Imaging Testing is not routinely needed, but fungal cultures may be helpful in resistant cases.

Special Testing Biopsy may be done when the diagnosis is uncertain.

Differential Diagnosis Psoriasis, atopic dermatitis, rosacea, pityriasis versicolor, tinea, contact dermatitis, lupus.

Treatments

Behavioral Thick scales (such as in infantile SD) may be loosened by application of oil to loosen the crust then shampoo to rinse off. In adults, lid and facial hygiene should be performed with antidandruff shampoos.

Medications Medications for SD include antifungals, steroid agents, and keratolytic agents [6].

Face: ketoconazole 2 % cream or foam bid × 4 weeks, ciclopirox (Loprox) 1 % cream, metronidazole (Metrogel) 0.75 % gel. Low-potency topical steroids (Table 1) are used to decrease inflammation: Hydrocortisone 1 % cream/lotion, desonide (DesOwen) lotion twice daily for several days, and calcineurin inhibitors such as tacrolimus 0.1 % ointment and pimecrolimus 1 % cream bid × 8 weeks also decrease inflammation.

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Scalp (antifungal): ketoconazole 2 % shampoo (1 % is over the counter (OTC)), selenium sulfide shampoo 2.5 % (1 % OTC), ciclopirox 1 % shampoo.

Topical steroids: clobetasol 0.05 % shampoo/foam twice weekly for 1 month, fluocinonide (Derma-Smoothe) 0.05 % solution, desonide (DesOwen) 0.05 % lotion.

Oral antifungals may be needed in resistant cases: itraconazole 200 mg daily, ketoconazole 200 mg daily, or fluconazole 150 mg daily for 1–2 weeks.

Keratolytics: Lipohydroxy acid and 1 % salicylic acid shampoos have been effective.

Tea tree oil has also been shown to be more effective than placebo in studies [3].

Referrals Consultation with dermatology may be needed in resistant cases, which are more common with coexisting medical conditions such as HIV and neurologic disease.

Counseling Patients should be warned of the need to contact their provider if infectious symptoms occur.

Patient Education Physicians must explain to patients that SD is a chronic recurring condition and maintenance is often necessary with increases in frequency or strength of treatment when exacerbations occur. Treatment failures are often due to short length and insufficient frequency of treatment.

Papulosquamous Disease

Psoriasis

General Principles

Definition Psoriasis (PS) is an immune-mediated inflammatory genetic disease of dysregulated inflammation. Susceptibility genes have been mapped on several different chromosomes [7]. The skin condition is variable in severity. In addition, psoriasis may have systemic manifestations with the possibility for destructive seronegative arthritis that is independent of skin disease severity. Arthritis usually develops 12 years after the skin manifestations and affects up to 60 % of psoriasis sufferers [7]. Nail disease affects 50 % of psoriasis sufferers and is difficult to treat. Use of biologic and immunosuppressive agents has been a great advancement in the treatment and prevention of complications of psoriasis.

Psoriasis has been associated with other autoimmune conditions such as Crohn's disease and ulcerative colitis. Recent research has found associations with metabolic syndrome and cardiovascular disease. Common comorbidities are obesity, diabetes, coronary artery disease, hypertension, and an atherogenic lipoprotein profile [7].

Epidemiology PS affects 2 % of the population and is more common in patients that are overweight [7]. Genetic and environmental factors influence its development. The prevalence is increasing likely due to the increasing incidence of obesity. The age of onset is usually between 15 and 30 years of age, and the clinical course can be varied. There is another peak of diagnosis in the 55–60 age range.

Classification **Plaque psoriasis** is the most common form of PS and can vary from several hidden lesions to numerous plaques that may be difficult to hide and can lead to social isolation [2, 5, 7]. Plaques are typically one to several centimeters in size, round or oval shaped with a scale upon a red base. They most commonly occur on the extensor surfaces of arms and legs and can affect the buttocks and trunk.

Erythroderma is widespread erythema and is associated with systemic symptoms such as fever, chills, potentially a more severe hypothermia, and dehydration.

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Pustular psoriasis is a variation with pustular psoriatic lesions containing collections of neutrophils. There's also a localized variant with pustules confined to the palms and soles.

Guttate psoriasis is subcentimeter papules on the trunk or proximal extremities; it typically affects patients under 30 and often occurs after an upper respiratory strep infection.

Inverse psoriasis occurs on flexural and skinfold areas.

Diagnosis

History Patients will typically report seeing areas of skin that appear inflamed and scaly on the scalp, elbow, or knees and do not resolve with time. Plaques and pustules may be painful. Some patients may complain of joint pain from associated arthritis. Lymphoma and melanoma have an increased prevalence as well as squamous cell carcinoma with patients that have extended UV treatment [7]. Depression and suicidal ideation are common among psoriasis sufferers. Psoriasis is increased among those who abuse alcohol, but it is unknown if this is a cause or an effect.

Physical Exam Classic psoriasis consists of 1–6 cm round or oval plaques of silvery scaling skin on a red base often over extensor surfaces. The Auspitz sign is pinpoint bleeding which occurs after peeling back the scale. Guttate psoriasis presents with very small plaques 1–10 mm in diameter. Pustular psoriasis will present with pustules over the body or palms and soles. Erythrodermic psoriasis presents with generalized erythema over the entire body; scaling may or may not be present. Nail disease can include pitting, onycholysis, and subungual hyperkeratosis. The majority of patients with psoriasis will have some nail involvement during their lifetime more commonly in the fingers.

Lab and Imaging Studies do not add to diagnosis or prognosis.

Special Testing Punch biopsy can verify the diagnosis if it is uncertain.

Differential Diagnosis Atopic dermatitis, lichen planus, contact dermatitis, T-cell lymphoma, pityriasis rosea, scalp seborrheic dermatitis, tinea.

Treatment

Medications Limited disease (less than 5 % of the skin) can generally be treated with topical medications [8]. Topical steroids (TSs) can be quite effective when tailored toward the patient including thought to vehicle delivery depending on the body part affected and patient preference. Low-potency steroids should be reserved for areas with thin skin such as the face and intertriginous areas. Mid- or high-potency steroids are the typical choice for initial therapy, and underdosing with a lower strength is more likely to lead to treatment failure. These treatments should be limited to 4 weeks of use with reduction in frequency as response occurs. Calcipotriene 0.005 % (Dovonex) [8], a vitamin D analog, works by inhibiting keratinocyte proliferation; it is available in cream and lotions and in combination with steroids. The most common side effect is local irritation and dryness, and its use is inactivated by UVA light. Calcitriol and tacalcitol are newer formulations that will likely be available in the United States soon. Combination treatment with calcipotriene and steroid ointment can also be helpful.

Topical calcineurin inhibitors, tacrolimus and pimecrolimus, alter the inflammatory cascade [8] and can be useful especially for treatment in thin-skinned areas and when used under occlusion. Tazarotene (Tazorac) 0.1 % qhs can also be helpful but can be limited by local irritation.

Topical coal tar also affects keratinocyte proliferation [8] and is commonly prescribed in other countries; however, its use is not well tolerated due to the odor and potential staining of clothes.

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Extensive disease affecting greater than 5 % of the skin typically requires a combination of topical therapy, light therapy, and systemic therapy [8].

Systemic therapy can prevent or halt the progression of complications such as psoriatic arthritis. Acitretin (Soriatane) and isotretinoin are oral retinoids that are effective, but both are teratogenic. Immunosuppressive agents such as methotrexate and cyclosporin (CyA) have been useful. Biologic agents are FDA approved for psoriasis; there are multiple agents that are currently in use and many in the pipeline. Prescribers must be familiar with side effects of each medication as they work through immunosuppression. The physician should understand pretreatment screening tests, vaccinations needed for patients undergoing immunosuppressive treatment, pregnancy prevention, and lab surveillance. Discussion of biologics is beyond the scope of this chapter and rapidly changing.

Phototherapy with narrowband UVB can be effective but requires treatment several times a week [8]. Psoriatic ultraviolet A (PUVA) is very effective and can lead to long-term remission in some people. However, this may be associated with photoaging and potential increased risk of skin cancer.

Referral Dermatology consultation is highly recommended in psoriasis that is extensive (>5 % of skin) or has been difficult to treat. The physician should keep in mind that complications of psoriasis are independent of skin disease severity.

Counseling The physician who prescribes systemic therapy should warn the patient of increased risk of infection if immunosuppressive therapy is used.

Patient Education The physician should impress upon the patient that they have a chronic disease that will require maintenance therapy. Patients should be screened for social complications such as isolation and depression.

Acne

General Principles

Definition Acne is a recurrent inflammatory condition that often starts in preadolescence or adolescence. It is typically more severe in adolescents but can continue on into adulthood. Acne is thought to be a combination of variations in skin oiliness, hormonal changes, increased testosterone levels, and bacterial colonization [9]. Although diet is often blamed, it has not been shown to be a factor in the severity of the disease [10].

Epidemiology Acne occurs in all ages but is much more common in adolescents. Most people will have acne at some point in their lifetimes. It occurs in all races.

Classification Acne can be classified according to age or predominant skin findings [10].

Preadolescent acne occurs between the ages of 7 and 12 generally preceding puberty and most commonly occurs in the forehead and midface areas.

Adolescent acne occurs between the ages of 12 and 19 and can vary in intensity and area affected. This is usually the time of the most severe acne.

Adult acne occurs at any age; it is usually milder and distinctly different from rosacea. Women may experience varying acnes throughout their menstrual cycle which is often referred to as hormonal.

Lesion classifications include **comedonal** with closed comedones (whitehead) or open comedones (blackheads).

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Mixed comedonal/inflammatory will have a combination of each.

Cystic nodular acne consists of deep painful cyst that may lead to scarring.

Acne fulminans is a rare condition with sudden onset of severe crusting acne and systemic illness [2] (Photo 1).

Approach to the Patient

Diagnosis and treatment will often include counseling the patient and parents. Treatment may be a combination of parental assistance and adolescents independently being responsible (or irresponsible) for their own treatment. Assessments of treatment failures should include these realities.

Diagnosis

History Most patients will come to the physician after having acne for some time. History should include type of acne lesion they have seen, OTC product use, soap use, hygiene habits, and which areas have been affected. Family history of scarring acne may be a clue to the potential severity and need for close follow-up.

Physical Exam Inspection of the skin may show closed comedones, open comedones, cysts, and inflammation. Physical exam should include examination of the chest and back.

Differential Diagnosis Rosacea, folliculitis.

Treatment

Behavioral Patients should be instructed to wash their face twice daily and not to use very astringent products.

Medications Treatment choices are aimed at the type of acne and should include a stepwise approach starting with topical antibiotics such as benzoyl peroxide, adding a topical tretinoin or considering change of topical therapy, then adding oral antibiotics, and then Accutane.

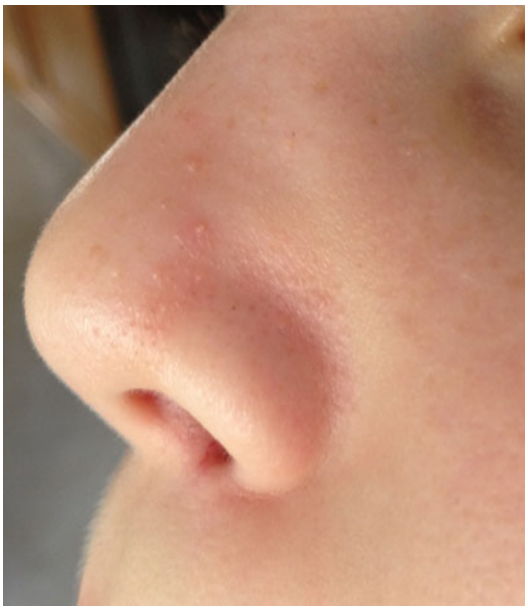

Photo 1 Closed comedonal acne in a preadolescent

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Table 2 Adolescent acne treatment

Severity	Initial	Inadequate response
Mild	BP or TR or Combo Tx, BP + TAbx or TR + TAbx + BP	Add BP or retinoid or increase TR strength
Moderate (comedonal/mixed/inflammatory)	TR + BP or TP + BP + oral Abx	Increase TR strength/type or add/change OAbx or OCP^{female}
Severe (inflammatory/nodular)	Oral Abx + topical retinoid + topical Ab	Change OAbx or isotretinoin or OCP^{female}

See Refs. [2, 5, 9, 10]
TR topical retinoids: tretinoin, adapalene, tazarotene
TAbx topical antibiotics
BP benzoyl peroxide, clindamycin, erythromycin, sulfacetamide
OCP oral contraceptives
OAbx doxycycline, minocycline, tetracycline

Topical antibiotics (TAbx) work by decreasing the colonization of *Propionibacterium* acnes [10], benzoyl peroxide (BP) 2.5–10 % (cream, gel OTC) with stronger concentrations being more irritating and sodium sulfacetamide (Sulfacet-R). Clindamycin (solution, gel, lotion) and erythromycin (solution, gel) should not be used alone as they can create bacterial resistance. Combination of topical antibiotics containing BP may cause less resistance.

Topical retinoids (TR) reduce follicle obstruction [10] and can cause irritation so dosing strength and vehicle should be gradually increased: tretinoin 0.025 %, 0.05 % (Retin A, gel, cream), adapalene 0.1 %, 0.3 % qhs (Differin, gel, cream).

Tazarotene 1 % cream qhs (Tazorac) – stronger, more irritating.

Comedolytic agents: salicylic acid (Clearasil, Clean and Clear OTC), azelaic acid (Azelex) 20 % cream 15 % gel (comedolytic/antibacterial).

Systemic antibiotics are indicated in resistant cases [9] but have been overused in the past without trying topical therapies initially (doxycycline 100 mg daily/bid, minocycline (Minocin) 100 mg daily, tetracycline 500 mg daily/bid, erythromycin 250–500 mg bid, trimethoprim/sulfamethoxazole bid); bacterial resistance is common with oral antibiotic use, and most cannot be used in pregnancy.

Oral retinoids: Isotretinoin (Accutane) 5–2.0 mg/kg/day [9, 10] is very effective. Isotretinoin (Accutane) can be a helpful addition to the acne arsenal in resistant cases or severe nodular acne; however, it is vital that providers familiarize themselves with the standard of care when consenting, monitoring, and prescribing this medication. Common side effects include severe dry skin, dry mucous membranes and eyes, and headaches. Complications are depression, liver and cholesterol abnormalities, and severe birth defects if a fetus is exposed. Currently, prescribing isotretinoin to females of childbearing age requires a physician to register themselves and the patient in the iPLEDGE system [11]. iPLEDGE is a manufacturer-supported FDA-approved risk management system that strives to prevent fetal exposure to isotretinoin in female patients [12]. It is vitally important that one is familiar with lab surveillance: lipids, LFTs, CBC, and birth control use.

Oral contraceptives: Norgestimate/ethinyl estradiol (Ortho Tri-Cyclen) and norethindrone acetate/ethinyl estradiol (Estrostep) have been FDA approved, but almost any OCP will work.

Antiandrogens: Spironolactone 50–200 mg/day antiandrogen is also used.

Intralesional Steroids Triamcinolone 10 mg/ml (Kenalog) 0.1 ml injected directly into nodule can reduce the size of the nodule.

Referral Referral to dermatology should be considered in treatment failures and in patients with cystic scarring acne, as they may be good candidates for Accutane. Endocrinology referral may be

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indicated in cases where endocrine dysfunction is suspected, very young age, or unexpected increase in severity.

Counseling Patients taking acne medications that are teratogenic should be counseled on proper birth control.

Patient education Acne sufferers should be instructed in proper hygiene and need for daily treatments to ensure response. Clinicians should monitor mood in teenagers and people with severe acne which is associated with depression.

Rosacea

General Principles

Definition Rosacea is a chronic inflammatory condition of the oil glands of the face thought to be due to bacterial colonization and skin susceptibility [2]. It is characterized by flushing of the skin due to capillary reactivity. Rosacea causes chronic redness of the face, adult acne-like lesions, and sensitivity to temperature change. Ocular involvement can occur.

Epidemiology It is more common in Caucasians of Irish, English, or German descent and more prevalent in females [13]. The symptoms typically start after age 30.

Classification **Erythematotelangiectatic** Classic type with redness and telangiectasias.

Papulopustular Pustules are predominant.

Rhinophymatous More common in males; the nose and face develop thickened skin.

Ocular rosacea A variant with eye redness and sensitivity.

Diagnosis

History Patient will typically complain of gradual onset of sensitive skin characterized by flushing and stinging. They may report redness and worsening acne that does not resolve over time. Patients with long-standing rosacea may have noticed a thickening and distortion of the skin.

Ocular rosacea typically causes a feeling of foreign body sensation and photophobia, and some patients have recurrent hordeolum.

Physical Examination The most common finding is general redness over the cheeks, nose, forehead, and chin. Lesions can include papules and pustules but are not comedonal. Telangiectasias can be seen on close inspection. Phymatous rosacea will have thickened skin, enlarged pores, and telangiectasias. Ocular findings can include eyelid inflammation, conjunctivitis, and telangiectasias on the eyelids. Corneal ulcers can occur in severe cases.

Differential Diagnosis Acne, systemic lupus erythematosus (SLE), polymyositis, sarcoidosis, photodermatitis.

Ocular: bacterial conjunctivitis.

Treatment

Behavioral Treatments include avoidance of triggers such as alcohol, spicy food, or hot beverages. Exposure to the sun or extreme temperature changes can worsen symptoms. Patients should avoid astringents or substances that contain alcohol, menthol, peppermint, witch hazel, and eucalyptus. Cleansers should be fragrance free with a neutral pH. Patients should be urged to use sunscreen and cover the skin. Moisturizers help to restore the normal skin barrier.

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Medications Topical therapies [5, 13] include metronidazole (Metrogel, Noritate) 0.75–1 % daily and sulfacetamide with sulfur (Sulfacet-R) once daily.

Azelaic acid 1 % (Azelex) is used for papules, pustules, erythema, and nodules.

Oral tetracyclines are helpful for controlling inflammation in more severe cases: doxycycline 100 mg bid, minocycline 100 mg bid, and tetracycline 500 mg bid. They may be tapered after 1 month of treatment.

Isotretinoin (Accutane) may be effective.

Brimonidine tartrate (Mirvaso) 0.33 % topical gel [14] is a selective alpha-2 agonist aimed at decreasing erythema that works by decreasing blood vessel dilation.

Ocular rosacea is primarily treated with oral antibiotics, eyelid hygiene, and the use of metronidazole gel.

Lasers are effective for removing vascular telangiectasias.

Rhinophyma can be treated with a CO_2 laser or dermabrasion.

Referrals Dermatology consultation is recommended for patients that do not respond to therapy or have more severe cases or those requiring treatment with laser. Ophthalmology referral may be useful to confirm the diagnosis and necessary for proper treatment of ocular rosacea.

Patient Education Patients should be instructed about avoidance of triggers such as astringent soaps and fragrances.

Hidradenitis Suppurativa (HS) aka Acne Inversa

General Principles

Definition Hidradenitis is a chronic condition characterized by recurrent painful cysts in the armpit and groin areas. It is caused by intermittent hair follicle occlusion in areas with high numbers of apocrine glands [2]. The follicle becomes inflamed and may drain; severe cases will result in fistula and scar formation.

Epidemiology HS is more common in women typically starting after puberty.

Diagnosis

History Most patients will report recurrent painful lumps in the armpit or groin. The cysts may persist for some time or resolve some time after draining spontaneously.

Physical Exam The physician will be able to palpate tender nodules beneath the skin 5 mm to 2 cm in size. The skin overlying the lumps may be erythematous or warm; drainage may be seen. Advanced cases may show sinus tracts with thickened skin and hypertrophic scar formation.

Differential Diagnosis Acne, abscess, ruptured epidermal cyst.

Treatment

Large acute lesions should be incised and drained to give symptomatic relief.

Behavioral Patients should be instructed to bathe regularly and quit smoking.

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Medication Oral tetracyclines [5] are helpful for controlling inflammation in more severe cases: doxycycline 100 mg bid, minocycline 100 mg bid, tetracycline 500 mg bid. Cephalexin 500 mg tid is also helpful if overlying skin is infected.

Triamcinolone 10 mg/ml (Kenalog) 0.1 ml injected directly into a nodule can reduce the size of the nodule.

Referral Consultation with a dermatologist or general surgeon should be considered in complicated cases.

Counseling Patients should be warned of potential scarring for surgical procedures.

Patient Education Patients should be encouraged to lose weight if obese.

Contact Dermatitis

General Principles

Definition Contact dermatitis is a common skin problem that actually encompasses two distinct conditions: allergic contact dermatitis (ACD) and irritant contact dermatitis (ICD) [15]. The two conditions may be difficult to distinguish from each other on physical exam. History may be helpful in differentiation, or skin testing may be necessary.

Epidemiology Allergic contact dermatitis is slightly more common in females. Irritant contact dermatitis is common in occupations where exposures to irritants are likely to occur; these include the use of solvents and cutting fluids in machinery jobs and exposure to irritants in gardening, painting, photography, hairdressing, food processing, health, and beauty professions [16].

ICD is the second most common work-related reason for needing medical attention after trauma.

Classification **Allergic contact dermatitis (ACD)** is an allergic reaction to an antigen that becomes immunogenic after contacting proteins in the skin [16]. It is a delayed hypersensitivity reaction that typically occurs several days after an exposure. Reexposure leads to sensitization and quicker onset of rash. The reaction occurs only when the substance came in direct contact with the skin or was transferred to another part of the body by touch. Common causes are *Toxicodendron* (rhus) plants – their urushiol sap is found in poison ivy, oak, and sumac – and nickel, a common component of cheaper jewelry and metal belt buckles. Fragrances, balsam of Peru, and cosmetics commonly cause ACD on the face and thin skin of the neck and arms. Adhesive tape, topical medicines, lanolin, neomycin, and nonsteroidal anti-inflammatory drug (NSAID) creams are also frequent offenders. Latex found in toys and balloons can also cause ACD.

Irritant contact dermatitis (ICD) is caused by repetitive exposure to a substance that chemically irritates or damages the skin [16]. Subsequently, a chemical exposed to already damaged skin will cause a subsequent immune reaction. Chemicals found in the workplace or in repeated exposure in the home during hobbies are most likely to cause these reactions. Reactions most often occur on the hands. Common causes are solvents, cutting fluids, photography chemicals, and detergents. Specific substances the physician may ask about when investigating the cause include chromium, rubber additives, nickel, food ingredients, latex gloves, and bisphenol A in vinyl gloves. Lip licking and repeated handwashing can damage the skin and predispose patients to becoming irritated by chemicals.

Eyelid dermatitis (ED) [16] is a subset of contact dermatitis that can be caused by direct exposure of a substance to the eyelid or commonly transfer of an allergen or irritant chemical. Frequent offenders are cosmetics and manicuring products. ED can also be caused by allergens in the air or cosmetics applied to other areas then transferred to the eyes as they are often touched throughout the day.

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Table 3 Common contact allergens

Area	Allergen source	Substance
Eye	Cosmetics, nail polish, and hair product components	Acrylic, formaldehyde multiple chemicals in hair treatments
Scalp	Hair dye	Paraphenylenediamine
Hands	Fragrance work/hobby chemicals	Chromium, nickel, rubber additives, latex – natural rubber vinyl gloves – bisphenol A
Lips	Lip balm	Cinnamon, peppermint
Genitals	Topical meds, lubricants	Latex – condom/diagram
Neck	Jewelry, hair dye, perfumes	Nickel
Axilla	Shaving, depilatory agents	Aluminum hydroxide
Face	Fragrance, sunscreen, rubber, balloons, toys, sponges	Latex, balsam of Peru, nickel (ears)
Legs	Depilatories, topical medications	Topical steroids/neomycin, thimerosal/caines (with chronic stasis)

Allergic contact cheilitis[16] occurs in patients that are prone to chapped lips wherein the dry fissured lips allow antigen exposure. Common sources are lip balm, cinnamon, and peppermint (Table 3).

Diagnosis

History The ACD rash typically follows exposure within 24–96 h. Subsequent exposure results in a quicker onset of rash. The rash typically starts with a mild itch or burn, and then pruritus increases and can be very intense. A complete history of potential exposures to the affected areas within the week prior is helpful. Even with a good history, patients often do not recall all exposures. If ICD is suspected, a thorough work history is important. Common professions that predispose patients to ICD are health professionals, food industry workers, beauticians, hairdressers, machinists, construction workers, agricultural workers, foresters, and fishers. A home history of hobbies such as photography should also be investigated including all chemicals and what area of the body is exposed.

Physical Exam ACD will typically appear like scaly, red well-demarcated patch. Clustered papules and vesicles or bulla may be present. Plant dermatitis is typically a linear vesicular rash (Koebner reaction). Early stages of ACD are more likely to be characterized as papular vesicular eruptions, while a chronic contact will include the later stages of hyperkeratosis, lichenification, fissuring, and scaling. The dorsum of the hand is a common site as well as any area that may have come in contact with the irritant. It is unusual to have ACD on the palms or soles as the skin is thick and not easily penetrated by an antigen. ICD can appear similar but is more likely to be lichenified and not as well demarcated.

ACD will typically resolve within 2–4 weeks but may last as much as 1–2 months. In ICD, skin changes can persist as long as the irritants are repeatedly in contact with the skin.

Laboratory Tests They are not usually needed; however, a KOH test may be helpful to rule out a fungal infection.

Special Testing Biopsy may be required to diagnose the condition. ACD typical pathology will show spongiotic edema and perivascular inflammation with a histiocytic infiltrate. ICD may show necrosis, acantholysis, and pustulosis.

Patch testing[16] is indicated when the cause is not obvious or recurrent symptoms occur. It is very important in occupational exposures where the patient may have to use a special equipment to keep from coming in contact with the irritant. Patch testing cannot be done when a patient is on more than 20 mg of

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prednisone or on an area that has been treated with a potent topical steroid or calcineurin inhibitor within 1 week of testing. It is subject to false positives especially in atopic patients.

Differential Diagnosis Atopic dermatitis, lichen simplex, neurodermatitis, psoriasis, impetigo, erythrasma, scabies, nummular dermatitis, mycosis fungoides, cutaneous drug reaction.

Treatment

Behavioral Avoidance of allergic agents is the mainstay of ACD treatment, when this is not practical protecting the area from direct exposure through creating a barrier such as sewing a piece of fabric over the nickel metal on jeans snaps or belt buckles. Treatment of the skin rash commonly starts with cool compresses to soothe the symptoms. Burow's solution, calamine, and oatmeal solution can also be helpful.

Medications Small areas of the skin can be treated with mid- or high-potency topical steroids; thinner skin areas should be treated with lower-potency TS.

Oral steroids [16] are a reasonable option when an extensive area is involved. It will offer relief within 12–24 h. The typical starting dose is 0.5–1 mg/kg for 5–7 days then decrease to 50 % of the dose for an additional 5–7 days.

Antihistamines can help by sedating patients but have not been shown to ease symptoms. Topical steroids are not as effective in ICD.

Emollients are the main treatment for ICD as a secondary prevention to repair the skin barrier and decrease the drying and cracking of the skin that aids or worsens the skin irritation.

Referrals Dermatology consultation is helpful when patch testing is needed.

Patient Education Physicians should instruct patients in avoidance of substances and help them understand where they may be able to find substances.

Urticaria

General Principles

Definition Urticaria is a condition characterized by wheals and hives that appear intermittently and are associated with severe itching. It can be caused by IgE-mediated allergic reactions and non-IgA-mediated mechanisms [17]. Both will cause mast cell and basophil activation. A hive is consists of superficial edema of the epidermis. Severe reactions may include systemic symptoms such as fatigue, malaise, and gastrointestinal disturbances. Angioedema may also occur. In many cases, no cause can be found [18].

Common causes: medications such as antibiotics, opioids, NSAIDs, ACE inhibitors, and radiocontrast agents

Children and adults: viral infections, rotavirus, rhinovirus, mycoplasma group A strep, antibiotics, and IgE-mediated reactions to food such as milk, eggs, and wheat

Adults: tree pollen, peanuts, seafood, vaccinations, insect stings, inhalant allergens

Epidemiology Urticaria is most common in young adults aged 20–40 [17]; in chronic urticaria, there is a female preponderance.

Classification **Acute urticaria** Duration is <6 weeks. It is more likely to be associated with a virus and responsible for 2/3 of urticaria.

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Chronic urticaria (**CU**) Duration is >6 weeks of recurrent hives and in most cases, a cause cannot be found. Etiology can be hepatitis B, Epstein Barr virus (EBV), HSV, *Helicobacter pylori*, and parasite infections [17]. There are medical conditions associated with CU – such as cryoglobulinemia, hepatitis C virus, lymphoproliferative disorders – Chronic Lymphocytic Leukemia (CLL), connective tissue disease, SLE, Juvenile Rheumatoid Arthritis (JRA), serum sickness, thyroid disease, hormone therapies (OCPs, neoplasms, ovarian tumors).

Types of Urticaria **Physical urticaria** (dermatographic urticarias) – can persist for years [18].

Vibratory urticaria – itching and swelling after the skin is exposed to vibration.

Solar urticaria – patients will have urticaria within several minutes of exposure to sunlight.

Delayed pressure urticaria – swelling several hours after exposure to a skin pressure. Common causes are tight garments, working with tools.

Cold urticaria – development of hives in response to a cold contact.

Heat urticaria – development of hives in response to ambient heat.

Aquagenic urticaria – rare, appearance of hives after direct contact of the skin with water.

Cholinergic urticaria – small hives that occur as body temperature rises; it can be caused by exercise, sweating, hot baths or showers, or embarrassment/flushing.

Exercise-induced anaphylaxis (EIA) – pt develops itching with hives and angioedema after exercise; in some patients, this is related to ingestion of a specific food or medication and exercising afterwards; in others, exercise alone may cause it.

Contact urticaria – latex, stinging nettle.

Diagnosis

History The physician should take a thorough history of recent exposure to medications, food, acute infectious symptoms, and aeroallergens. One should inquire as to whether the rash appears transient, the history of previous similar rash, and the timing of symptoms. Symptoms of anaphylaxis may be present such as difficulty of breathing, light-headedness, or gastrointestinal (GI) symptoms. Angioedema should be ruled in or out, and symptoms consistent with recent exposure to physical urticarias should be elicited. Past medical history should be taken with attention to the history of autoimmune or inflammatory disorders.

Physical Examination The typical hives will be 1–4 cm in size, various shaped, and pink or red in color and will blanch with pressure. A hive/wheal will consist of raised skin that is erythematous and firm; dermatographism is often present. The wheals will usually appear and resolve in minutes to hours, but some may remain and then regress within 24–48 h; in the meantime, new ones may form. The physician should examine for angioedema, a more diffuse swelling of the mucous membranes. Lung exam should be done to rule out stridor or wheezing.

Lab and Imaging Testing for causes of acute urticaria is generally not indicated unless there is a compelling reason [18]. In chronic urticaria, it is recommended that testing be done if disease is severe or persistent although it is unlikely to find a cause.

Recurrent urticaria with angioedema may be a sign of hereditary angioedema, and testing for acquired C1 inhibitor deficiency or angiotensin-converting inhibitor should be done.

Common labs are complete blood count (CBC) to detect eosinophilia; ESR (erythrocyte sedimentation rate) can be elevated in autoinflammatory disorders or vasculitis, *H. pylori*, thyroid autoantibodies.

Complement screening – C1 inhibitor deficiency.

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Special Testing Skin testing immunoassays may help to determine the cause in acute cases. Biopsy is typically not needed but if performed will show a lymphocytic infiltrate or a mixed cellular infiltrate of lymphocytes and inflammatory cells. Biopsy should be done if the diagnosis is unclear and if vasculitis is in the differential. Food challenge testing can be done for specific urticarias.

Cold urticaria – ice cube to the forearm for 5 min.

Delayed pressure urticaria area – 15 lb of weight suspended over the patient's shoulder for 15 min then should be recorded if whether a reaction develops minutes to several hours later.

Dermatographia – can be brought about by stroking the skin with a firm object and seeing if a skin reaction is evoked.

Aquagenic can be diagnosed by applying a wet compress for 20 min.

Differential Diagnosis Cutaneous drug reaction, anaphylaxis, erythema multiforme, viral exanthem, Stevens-Johnson syndrome, urticarial vasculitis.

Treatment

Behavioral Avoidance of known allergies.

Medications Second-generation antihistamines for 4–6 weeks [18] then tapered: cetirizine (Zyrtec) 10 mg daily, fexofenadine (Allegra) 180 mg daily, loratadine (Claritin) 10 mg daily. Doubling or quadrupling the usual dose can be helpful for patients who do not respond to initial dosing.

First-generation antihistamines may be limited because of sedation: diphenhydramine (Benadryl) 25–50 mg qid prn, hydroxyzine 25–50 mg qid prn.

Oral steroids may be effective: prednisone 40–60 mg daily 1–3 weeks.

H_2 antagonist: ranitidine (Zantac) 150–300 mg bid, famotidine (Pepcid) 20–40 mg bid, montelukast (antileukotrienes) (Singulair) 10 mg daily.

Biologics: Omalizumab 150–300 mg subQ for chronic urticaria is FDA approved for patients with CU that are not improved with other treatments.

Referrals Consultation with an allergist or dermatologist may be necessary for refractory or persistently recurring urticaria.

Patient Education Physicians should counsel patients in avoidance of triggers and that NSAIDs may worsen symptoms.

Pityriasis Rosea (PR)

General Principles

Definition PR is a self-limited acute exanthem that is thought to be caused by infection; however, no specific virus or bacteria have ever been found [19]. Outbreaks have occurred in clusters, and PR will not typically recur.

Epidemiology It most commonly affects children and young adults.

Diagnosis

History Patients will typically complain of a rash that started on their trunk and can spread variably to the limbs. Some patients will complain of mild itching and in some cases will remember a prodromal illness.

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Physical Examination Inspection of the skin will typically show oval raised patches 5–10 mm in size with a dry collarette of scale on the periphery. Coloring can be mild pink and appear lighter than the natural skin color in darker-skinned individuals. The rash typically begins over the torso and is aligned in a typical Christmas tree pattern that will spare the hands. A herald patch may precede the diffuse rash by days to weeks in 50 % of the cases; it will measure 2–10 cm. The physical exam should include auscultation of the lungs to rule out wheezing or stridor which may also be seen in allergic drug reactions.

Laboratory KOH testing is not necessary but if done will be negative.

Special Testing Biopsy is rarely needed as patients can typically be reassured but can be done at a later date if the rash does not resolve as expected. Histology will show nonspecific inflammation.

Differential Diagnosis Tinea corporis, secondary syphilis, eczema, guttate psoriasis, other viral exanthems, cutaneous drug reaction.

Treatment
Behavioral The mainstay of therapy is reassurance as in the majority of patients the rash will recede within 5 weeks and in some it may last as long as 3 months.

Medications In some patients, pruritus is bothersome and treated with topical steroids. Calamine lotion and zinc oxide oral antihistamines may be helpful. Systemic steroids may be used in cases where itching is severe.

Referral This should not be needed.

Patient Education Physicians should reassure the patient that the rash will resolve, not scar, and not recur.

Cutaneous Drug Reaction (CDR)/Cutaneous Drug Eruptions

General Principles

Definition Eruptions comprise a group of immune- and nonimmune-mediated reactions that manifest as several different cutaneous reactions.

Epidemiology Cutaneous reactions are more common in older patients and women. Certain comorbidities, for instance, renal insufficiency, lupus, hepatic disease, cystic fibrosis (CF), and human immunodeficiency virus (HIV), may predispose patients to reactions. UV light can increase the adverse reaction as well as infections like mononucleosis, herpes simplex virus (HSV), or mycoplasma [20].

Classifications Allergic reactions are of the following types: IgE-mediated hypersensitivity Type I, cytotoxic antibody Type II, vasculitis immune complex reaction Type III, and delayed hypersensitivity Type IV [20].

Exanthem maculopapular rashes – most common reaction with macules and papules more commonly concentrated on the torso.

Urticaria – intermittent hives.

Erythema multiforme (EM) – skin rash with targetoid lesions.

Angioedema – swelling of the lips and mucous membranes.

Drug-induced vasculitis – petechial rash.

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Fixed drug eruption – recurring skin reaction that is limited on the body geographically and recurs with repeated use of a medication.

Pigment changes – induced by some medications and can vary from melanotic to blue, silver, yellow, or red.

Photodermatitis drug + UV light – phototoxicity drug acts to concentrate UV in the skin and cause sunburn like rash.

Stevens-Johnson syndrome (**SJS**) 5 % mortality – a hypersensitivity reaction with blistering and desquamation.

Toxic epidermal necrolysis (**TEN**) 20–30 % mortality – blistering rash with significant desquamation.

Warfarin skin necrosis – rare hemorrhagic bulla while heparin necrosis is a more localized reaction with purpuric plaques near injection sites.

Diagnosis

History The physician should be concerned about any new rash in a patient who does not have a preexisting skin condition and who takes medication. Rashes are more likely to occur with topical application and oral ingestion and with chronic or repeated prescription. Exanthems typically start within 1–2 weeks of starting a new drug, but the range can be 1 week–1 month in medication-naive patients [21]. Repeated exposures to medications will result in a shorter time to onset of rash. Urticarial reactions can be immediate or within days of starting medication. The physician should review medication history, herbal history, previous reactions, and any improvement after discontinuation of the drug. Common drug offenders are carbamazepine, phenytoin, antibiotics, anti-inflammatory drugs, and allopurinol.

Physical Examination Presentation can be varied from exanthems that are maculopapular, morbilliform, or erythrodermic. Exanthems often occur first symmetrically on the torso and may be worse in areas under pressure like the back or buttocks in bedbound patients. Urticarial reactions can present with papules or large hives. EM presents with macules, papules, or vesicles that resemble a target. SJS will consist of blistering more extensively in multiple mucous membranes. TEN blistering and bulla will affect the skin and mucous membranes. Angioedema will present with swelling of the mucous membranes and possibly lips and if severe respiratory excursion may be difficult. Contact dermatitis will show erythematous urticarial plaques in areas of topical medication application.

Laboratory and Imaging For skin rashes, labs are not necessary, as CBC will generally not show eosinophilia. In more severe cases of TEN or SJS, laboratory testing is important to determine how ill a patient may be.

Special Testing Skin biopsy may be helpful, as the histology will show eosinophilia, edema, and inflammation. In erythema multiforme, vasculitis is seen and necrosis will be present. Biopsy will confirm the diagnosis if concern for SJS or TEN is present. Patch testing is helpful in contact dermatitis. Photopatch testing where exposure to UV light is added to patch testing is needed for photoallergic reactions. Skin prick test can confirm IgE-mediated allergic reactions; however, it should be done with proper precautions in patients with a history of severe reactions.

Differential Diagnosis Viral exanthem, pityriasis rosea, scalded skin syndrome.

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Treatment

Behavioral Exanthems are self-limited; however, many patients will request relief from symptoms. Discontinuation of the offending medication as well as documentation of the allergic reaction in the medical record is important.

Medications Treatment of symptoms includes antihistamines to help pruritus, topical steroids, and oral steroids. Second-generation antihistamines are cetirizine (Zyrtec) 10 mg daily, fexofenadine (Allegra) 180 mg daily, and loratadine (Claritin) 10 mg daily [20, 21]. First-generation antihistamine effectiveness may be limited by sedation: diphenhydramine (Benadryl) 25–50 mg qid prn, hydroxyzine 25–50 mg qid prn.

Oral steroids [21] may be effective: prednisone 40–60 mg daily 1–3 weeks.
Topical steroids may help in cases of contact dermatitis of discrete skin rash.
Hospitalization is necessary for SJS and TEN to perform fluid resuscitation.
Epinephrine may be necessary for angioedema and in cases of anaphylaxis.

Referral Consultation with an allergist or dermatologist may be needed when the specific causative medication cannot be found.

Patient Education Patients must be told that they are allergic to the medication and possible related medications; they must refrain from taking the medication again and should never take an unknown medication.

Bullous Diseases

Bullous Pemphigoid (BP)

General Principles

Definition Bullous pemphigoid (BP) is a chronic autoimmune disorder in which patients have recurrent bullous lesions on the skin. It is IgG mediated where autoantibodies bind to specific antigens causing a complement cascade resulting in blisters [22].

Epidemiology BP is more common in men over 60 years old [5].

Diagnosis

History Most patients will recall having itching prior to the formation of bulla, which, once formed, will take a long time to heal.

Physical Examination Lesions will have tense bulla/small blister overlying normal or erythematous skin. BP does not typically affect mucous membranes.

Special Testing Biopsy is necessary for diagnosis.

Differential Diagnosis Pemphigus vulgaris, scalded skin syndrome.

Treatment

Medications Oral steroids like prednisone 60–80 mg daily [2] then tapered after a few weeks may take 2–10 months for remission.

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IV immunoglobulin.

Immunosuppressive medications have been used for severe disease or when a patient has been unable to wean off of steroids.

High-potency topical steroids are applied topically for local disease.

Referral Dermatology consultation is necessary for patients who do not achieve an adequate response with systemic steroids or are unable to wean off steroids.

Counseling Patients on long-term steroids should be warned of the side effects of the treatment.

Patient Education Patients should be counseled of the chronicity of the condition and need to follow up with their physician.

Pemphigoid Vulgaris (PV)

General Principles

Definition PV is an autoimmune chronic bullous disease that affects the oral mucosa, skin, and mucous membranes. There is a high mortality rate of 10 % with treatment and higher without. It is caused by an autoantibody formed against the adhesive molecule that holds epidermis together; subsequent separation of keratinocytes then occurs [2, 5].

Epidemiology Age 30–50.

Classification **Pemphigus vulgaris** – common type

Pemphigus foliaceus – superficial form, more common in South America

Paraneoplastic pemphigus – a form associated with hematologic malignancies

Diagnosis

History Patients will report the appearance of painful blisters that typically start in the mucous membranes of the mouth, and then several weeks later, skin lesions will develop on the scalp, face, and upper torso.

Physical Examination Examination will reveal blisters that are of varying sizes, which easily shear off and leave painful erosion and then post-lesion hyperpigmentation. The Nikolsky sign is present when skin will shear off after lateral pressure is applied to the skin near a blister.

Laboratory and Imaging **Special testing** Two biopsies should be done via punch or shave that includes the epidermis. One biopsy should be sent for direct immunofluorescence, which will show desmoglein antibodies.

Differential Diagnosis Bullous pemphigoid, linear IgA dermatosis, dermatitis herpetiformis.

Treatment

Medications Oral steroids: prednisone 60 mg daily.

Referrals Consultation with multiple specialties may be needed: dermatology for treatment and gastroenterology for endoscopy if esophageal disease is suspected.

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Table 4 Amount of steroid to treat body surface area

Area	Fingertip unit
Hand	.5
Arm	3
Leg	6
Torso	8
Foot	2
Face	2

Counseling Patients on long-term steroids should be warned of the side effects of the treatment.

Patient Education and Activation Patients should be counseled of the chronicity of the condition and need to follow up with their physician.

Topical Steroid (TS) Treatment Principles

Steroid creams work by decreasing inflammation and hyperproliferation and altering immune reactions [4] (Table 1). They improve symptoms of itching and burning. TS is typically applied one to two times daily initially until response has begun, then decreasing the frequency of application.

Patients should be instructed in the amount of steroid to use. The fingertip unit [23] is the amount of steroid squeezed from a tube from fingertip to the first crease (Table 4).

Selection of the type of treatment and likelihood of it benefiting the patient should always be considered, as it will affect compliance [23]. Patients may prefer certain vehicles [3] so the physician should ask the patient whether they would prefer an oily substance versus cream or foam. In general, ointments are most useful for areas that are dry or where the skin is thickened or when its occlusive properties are beneficial. In these areas, creams may be rubbed off too easily; however, some patients may not like ointments due to their greasiness. Occlusion can be achieved by wrapping the area in plastic. Tape such as flurandrenolide (cordran tape) impregnated with steroid ointment is often used to treat areas such as the fingers. Creams are more useful in intertriginous areas and exudative lesions where they will not add too much moisture. Lotions are more easily applied to hair-bearing areas; they often contain alcohol. Gels can be drying which helps with exudative lesions. Foams and shampoos are more useful in hair-bearing areas like the scalp.

Undertreatment with low-potency steroid when a high-potency steroid is indicated (i.e., psoriasis) may lead to treatment failure [8] and affect adherence. In general, lower-potency steroids are used on areas with thinner skin such as the face and neck and in children. Moderate-potency topical steroids are used chronically in severe disease or thick skin such as the palms and soles.

High-potency TS is used in shorter durations and never on the face or intertriginous areas.

Side effects happen on occasion and comprise the following: tachyphylaxis, hypopigmentation, contact dermatitis to other ingredients in the vehicle, telangiectasia, striae, rosacea, and acne-like eruptions.

Adrenal suppression is possible when very high-potency steroids are used over extended periods of time. Skin atrophy is the most common effect of overuse which typically resolves after cessation of steroid.

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Family Medicine
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Skin Infections and Infestations

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Pyodermas and Bacterial Skin Infections

Impetigo

General Principles

Impetigo is a common, contagious superficial skin infection seen most often in infants and children.

Epidemiology It is caused by *Staphylococcus aureus* and Group A streptococci and presents in two major types: bullous and nonbullous. Bullous impetigo is caused by staphylococci that produce an epidermolytic toxin.

Diagnosis

Physical Examination Impetigo begins with small, thin-walled blisters that rapidly coalesce into round or oval-shaped bullae containing a cloudy fluid. The central area of the bullae then collapses, leaving a honey-colored thin layer surrounded by a rim of crusty tissue that continues to expand. In the untreated individual, these will reach 2–8 cm-sized patches that can remain for months. Nonbullous impetigo appears to be more related to Group A streptococcal infection, although staphylococci can also be found. Clinically, the lesions begin most often around the mouth or nose with small vesicles that rupture, producing a serious discharge that dries into a honey-colored crust. The lesions have a red, moist base and often extend by satellite lesions over adjacent skin.

Treatment

Treatment with topical 2 % mupirocin ointment is safe and as effective as oral antibiotics in patients with a limited number of lesions. Oral antibiotics are recommended for patients with numerous lesions or for infections that occur during community outbreaks of post-streptococcal glomerulonephritis to help eliminate nephritogenic strains of *Streptococcus pyogenes* [1].

Erysipelas and Cellulitis

General Principles

In contrast to impetigo, cellulitis and erysipelas are deeper skin infections manifested by distinctly painful, red, swollen skin.

Epidemiology The causative agents are predominantly Group A streptococci and *Staphylococcus aureus*, the latter presenting as either methicillin-sensitive (MSSA) or methicillin-resistant (MRSA) strains. Erysipelas is usually caused by Group A streptococci. It is a more superficial form of cellulitis.

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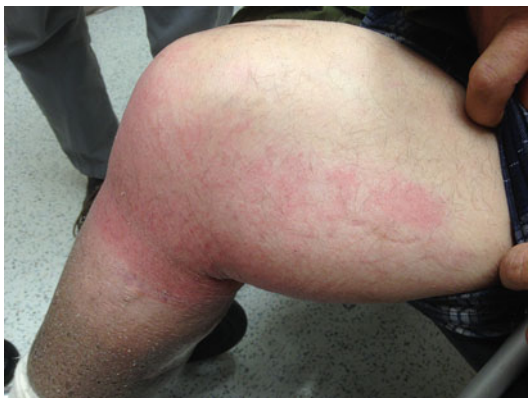

Fig. 1 Cellulitis in a patient with chronic edema and dry skin. Note the sharp inferior margin and streaking up the medial lymphatics. The skin was red, hot, and tender to touch

Diagnosis

Physical Examination Erysipelas has the clinically distinctive feature of a clear-cut margin that visibly demarcates the infected tissue from uninvolved adjacent skin. Lymphatic involvement is common and progression of the infection through the lymphatic chains causes linear "streaks," especially apparent on the extremities (Fig. 1). It is often associated with a fever of 101–104°, chills, and malaise.

Treatment

Treatment consists of oral or intravenous antibiotics active against streptococci, depending on the severity and location of the infection.

Cellulitis

General Principles

Cellulitis differs from erysipelas by involving deeper skin and subcutaneous structures.

Epidemiology

The past decade has witnessed a significant increase in the number of skin and soft tissue infections (SSTIs) reported worldwide from community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA). The development of such an infection can lead to cellulitis with or without abscess formation.

Diagnosis

Cellulitis is not clearly demarcated visually, as is erysipelas, but presents with pain, fever, and leukocytosis, usually with a demonstrable portal of entry. Lacking such a portal of entry, patients may report the initial tender papule was thought to be a "spider bite."

Laboratory Neither blood analysis (WBC, CRP) nor cultures of blood or skin aspirates has been found to be clinically useful or cost-effective in determining abscess presence [2].

Treatment

Treatment of cellulitis has become the subject for many studies related to CA-MRSA. The most recent recommendations are that empiric treatment of outpatient non-purulent cellulitis be initiated with

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β-lactam antibiotics (cephalexin, dicloxacillin, amoxicillin/clavulanate), finding no significant difference in clinical failure rates between these and non- β-lactam alternatives. The Infectious Disease Society of America (IDSA) has recently updated their guidelines (June 2014) for management of SSTIs. Their recommendations include the adoption of oral β-lactam antibiotics for the mild, non-purulent category and moving to intravenous antibiotics of similar nature for a moderate infection [3]. Individual community susceptibility data should always be considered in antibiotic choices.

Chemoprophylaxis The use of prophylactic antibiotics (benzathine penicillin or erythromycin or clindamycin) has been proven effective.

Prevention

Prevention of recurrent episodes of cellulitis is important, including physical inspection of the feet for interdigital maceration, cracks, or fissures.

Folliculitis, Furuncles, and Carbuncles

General Principles

Folliculitis is an inflammatory condition of the hair follicle, either from infection or superficial mild trauma, such as friction from clothing.

Epidemiology The bacterial etiology of infection is usually staphylococcal in nature. "Hot tub folliculitis" is a subset of folliculitis caused by *Pseudomonas aeruginosa,* which may be found in unclean hot tubs or jacuzzis.

Diagnosis

Physical Examination The condition presents as small white pustules at the site of hair follicles on almost any surface of the body. There is often a small ring of erythema around the infected follicle, and the lesion may be painless or variably painful depending on its size and depth. In skin that is repeatedly shaved, spread of the infection can occur quickly to multiple follicles from microtrauma and bacterial implantation.

Treatment

Treatment is effective with topical mupirocin ointment or with oral antibiotics in more extensive involvement. Razors must be changed frequently and shaving may need to be interrupted during treatment of the lesions. Hot tub folliculitis is usually self-limited and requires only antiseptic care.

Prevention

Decolonization techniques using mupirocin in the nares may help eliminate reservoirs of staphylococci.

Furuncles ("Boils")

General Principles

Furuncles ("boils") are localized infections that extend from a follicular site into a deeper, walled-off subcutaneous abscess. They are often found in areas of friction from clothing, such as the belt-line, groin, thighs, or bra-line, but also may occur near the nares or on the face [4].

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Diagnosis

Physical Examination Furuncles are characterized by an initially firm, tender erythematous nodule that subsequently enlarges and develops a fluctuant surface that erodes with spontaneous drainage.

Treatment

Treatment of furuncles is drainage, which may be encouraged spontaneously by warm compresses or may be accomplished by incision and drainage (I&D) under local anesthesia in the office. Oral anti-staphylococcal antibiotics are useful in the early stages of infection.

Carbuncles

General Principles

Carbuncles are multiple furuncles clustered together, characterized by larger areas of involvement and multiple drainage sites.

Treatment

Oral antibiotics and drainage procedures usually suffice, but surgical consultation may be required for extensive debridement.

Hidradenitis Suppurativa

General Principles

Hidradenitis suppurativa is a suppurative process affecting the follicles and apocrine glands in the axillae, groin, and below the female breasts that can seem to be a simple folliculitis early in its course. This disease progresses inexorably with gradual spread to adjacent follicles. After years, areas of scarred remnants remain scattered over the axillae, groin, and inframammary skin (Fig. 2).

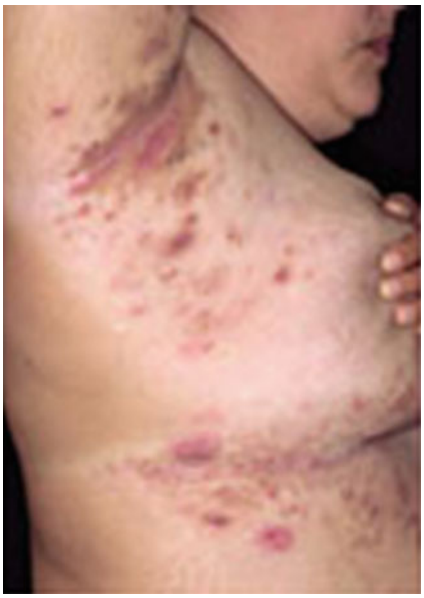

Fig. 2 Hidradenitis suppurativa

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Treatment
Treatment for individual drainage sites is similar to that of folliculitis, but the chronicity of the disease usually requires surgical removal of the affected areas.

Behavioral The impact of hidradenitis suppurativa on the emotional and psychological well-being of patients may require counseling and psychological support [5].

Abscess of Skin

General Principles
A skin abscess is the result of the accumulation of pus in the skin or subcutaneous tissues. Recent studies have shown that bedside ultrasonography improves diagnostic accuracy and decision-making regarding the presence of abscess fluid [6].

Diagnosis
Clinically, an abscess presents as an exquisitely tender, swollen, red, fluctuant mass. The diagnoses may be simple, but if accompanied by significant cellulitis, the indurated, tender tissue may make palpation of the fluctuant area difficult.

Treatment
The treatment of choice for skin abscesses is incision and drainage (I&D). The Infectious Disease Society of America (IDSA) recommends addition of non-beta-lactam empiric antibiotics only in moderate or severe categories of purulent skin and soft tissue infections (SSTIs) [3]. However, incision and drainage is a painful procedure, and a common mistake is to create an incision of insufficient depth to fully drain the abscess.

Referrals If local or regional anesthesia is inadequate, further sedation or anesthesia should be considered, especially for children or adults with abscesses that are unusually large or are in sensitive sites.

Prevention
Prevention of recurrent skin abscesses follows the rationale for that of recurrent cellulitis. Efforts at decolonization have not been shown in large studies to be statistically reliable. However, if attempted, a 10-day course of twice-daily intranasal mupirocin, daily hexachlorophene washes, and oral antibiotics (TMP/SMX or minocycline) aimed only at the index patient was shown to reduce the rate of methicillin-resistant *Staphylococcus aureus* (MRSA) reinfection in a small study in California [7].

Necrotizing Fasciitis

General Principles
Necrotizing fasciitis is an uncommon to rare life-threatening, rapidly progressive infection of the subcutaneous tissues and fascia.

Epidemiology It is most often polymicrobial (Type I), although a smaller proportion of patients will have only a single organism, usually group A streptococcus (Type II). A third type, recently described, is caused by vibrio species and is associated with salt water-related minor injuries (fish fin stings or handling raw sea food) in areas with warm seawater [8]. Predisposing factors include diabetes mellitus, cirrhosis, pulmonary disease, end-stage renal disease, immune suppression, or drug injection.

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Diagnosis

Clinical presentation is typically that of a presumed cellulitis. The only indicator that this may be more than a simple cellulitis is the finding of unrelenting pain that is out of proportion to the clinical findings. Without a high index of suspicion, the diagnosis may initially be missed and the patient sent home. As the disease progresses, the affected skin develops yellowish bullae, which become violaceous in color (a strong clue to the diagnosis of necrotizing fasciitis), and the skin becomes "woody" in texture, with loss of sensation. Crepitus may occur. Confusion and sepsis are frequent findings. The fatality rate is 25–70 % from sepsis and multiorgan failure.

Laboratory and Imaging Ancillary testing is nonspecific. Demonstration of gas or deeper tissue infection should prompt surgical consultation and immediate exploration to confirm or exclude necrotizing fasciitis.

Erythrasma

General Principles

This uncommon skin infection is characterized by brownish pigmentary change in a plaque-like area, usually in the groin, interdigital toe spaces, or inframammary areas.

Epidemiology The infection is caused by the bacteria *Clostridia minutissimum*, but is often confused with tinea, especially in the groin. It may remain for years if not treated appropriately. It can be distinguished by virtue of its less inflammatory presentation, relative lack of symptoms, and its coral red fluorescence with Wood's lamp [9].

Treatment

Treatment can be accomplished with oral erythromycin, or clarithromycin.

Cutaneous Leishmaniasis

General Principles

Cutaneous leishmaniasis is one of three forms of disease caused by an intracellular protozoa of the *Leishmania* species.

Epidemiology Leishmaniasis is transmitted by the sandfly, which is only 1/3 the size of a mosquito. Because it makes no sound, is small, and the bite may not be painful, patients often do not realize they have been bitten. Over 90 % of the cutaneous leishmaniasis originates in countries that are most often visited by military personnel, missionaries, or tourists. While the infection is rare in the United States, a persistent nodule or plaque on the torso, extremities, or face should prompt questions about exposure by travel to the Middle East, or to Central or South America.

Diagnosis

Physical Examination The patients present several weeks (or in some cases up to several months) after exposure with one or more non-pruritic nodules. The lesions progress to a nodular plaque and then often ulcerate with raised circular borders and a central depression. The lesions last for months and are usually painless.

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Differential Diagnosis Diagnosis can be made by a combination of clinical presentation and smears or biopsies from the active edge of a lesion [10].

Treatment

Treatment decisions should involve consultation with CDC and infectious disease consultants.

Viral Diseases of the Skin

Herpes Simplex

General Principles

Herpes simplex virus (HSV) is a neurotropic virus causing infections of the mucous membrane and skin.

Epidemiology The virus enters the tissues through a portal of entry on the skin or mucous membrane, replicates in the local site, and by retrograde axonal flow reaches the dorsal root ganglia, establishing a lifelong latency state. The primary infection can range from completely asymptomatic to a syndrome with significant pain and tissue change. Recurrent infections, always occurring at the same anatomic site, recapitulate the primary infection in a much-shortened course of about 1 week. The recurrences appear when the latent virus is reactivated by some stimulus, such as illness, fever, chapping, menses, or UV light exposure. Herpes simplex in wrestlers is called *Herpes gladiatorum* and is transmitted by direct contact during wrestling bouts. *Ocular herpes* is a rare cause of keratoconjunctivitis and can cause blindness. Emergent ophthalmologic referral is indicated if it is suspected. *Herpetic whitlow* is the infection by HSV of the distal phalanx around the nail or on the pulp of the finger tip. It occurs when the digit involved is exposed to HSV, either by thumb-sucking or digital-oral or digital-genital contact, in the presence of a portal of entry. *Eczema herpeticum* occurs when an atopic individual, often just recovering from an episode of herpes labialis, develops widespread HSV lesions over an area of recent eczema. This constitutes a dermatological emergency [11].

History The initial symptoms are a tingling pain or burning sensation at the site of infection, followed within days by local swelling and the appearance of uniform-sized groups of vesicles on a red base. These progress to umbilicated pustules, which then rupture and form crusts. The entire site is often very tender to touch.

Diagnosis

Physical Examination Herpes simplex labialis ("cold sore") is very common, and patients often do not seek the physician's care for recurrences (Fig. 3). Initial infections, particularly in infants and children, may cause enough oropharyngeal pain on swallowing to make fluid intake difficult.

Treatment

Treatment of primary and recurrent episodes on skin surfaces can be undertaken with topical creams such as acyclovir cream or n-docosanol cream (OTC Abreva) or with oral medications such as acyclovir, valacyclovir, or famciclovir.

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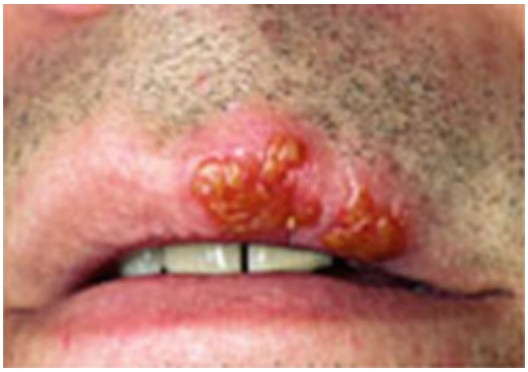

Fig. 3 Recurrent herpes on upper lip

Genital Herpes

Diagnosis

Physical Examination Genital herpes in the female can cause pain, itching and burning, dysuria, and discharge. In the male, pain and burning of the lesions may be associated with local lymphadenopathy.

Treatment

Treatment regimens are similar to that for oral lesions, but in pregnant females, the presence of an active HSV infection at or near delivery prompts concerns about vertical transmission to the fetus.

Prevention

A Cochrane review has shown that prophylaxis which begun with acyclovir or valacyclovir at 36 weeks gestation significantly reduces herpetic recurrences at delivery as well as reducing viral shedding [12].

Herpes Zoster

General Principles

Herpes zoster, commonly known as shingles, is a viral infection of the skin along the dermatome served by a dorsal root ganglion which was infected during a childhood episode of chicken pox. The virus remains latent until reactivated and then travels back down the sensory nerve and prompts the rash, which can occur anywhere along the dermatome.

History Clinically, the patient reports an initial sense of the skin itching or burning in the affected dermatome 4 or 5 days prior to the onset of the rash. Occasionally the area is so painful it can mimic more serious, internal diseases such as pleurisy, myocardial ischemia, or an intra-abdominal process, causing diagnostic confusion.

Diagnosis

Physical Examination The appearance of the classic erythematous rash, associated with the formation of variably sized blisters, along the course of the affected dermatome resolves any diagnostic dilemmas. The rash can continue to be painful in varying degrees as crops of blisters occur for a week. The thin-walled blisters rupture and form a crust, which gradually heals in 2–3 weeks [4].

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Treatment

Treatment of zoster is most successful when begun within 72 h of the onset of symptoms. Good results have been obtained with three oral medications: acyclovir (Zovirax), famciclovir (Famvir), and valacyclovir (Valtrex). Acetaminophen and nonsteroidal anti-inflammatories are useful for mild to moderately severe pain, whereas narcotic analgesics may be required in others. For postherpetic neuralgia, which occurs in a minority of patients but can be a serious problem, treatment options include tricyclic antidepressants, tramadol, long-acting opioids, or pregabalin (Lyrica). Topical capsaicin (Zostrix) or a lidocaine patch (Lidoderm) may also be of benefit.

Prevention

Prevention of herpes zoster by vaccination is indicated for patients over age 60 years [13].

Viral Warts

General Principles

Warts are caused by infection of the epidermis by the human papilloma virus (HPV), creating a variety of benign neoplasms. Most warts resolve spontaneously within months, but recalcitrant ones can last years. Cell-mediated immunity response is a key element in wart resolution, as witnessed by the more frequent and longer-lasting occurrences of warts in patients with AIDS, lymphomas, or immune suppressive drugs. There are a variety of treatments available, signaling that no single treatment regimen is always effective for cure.

Diagnosis

Physical Examination Common warts (*verruca vulgaris*) occur mostly on the hands and present as smooth, round papules that develop into typical dome-shaped round or ovoid lesions with hyperkeratotic, dry surfaces and loss of skin lines. Black dots, representing thrombosed vessels, may be seen on the surface or when exposed by paring down the keratinaceous surface with a #15 knife blade. Plantar warts occur on the soles of the feet in large, hyperkeratotic lesions that cause pain with walking. Trimming the thick keratin accumulation with a #15 knife blade relieves much of the discomfort. Condylomatous warts are found in moist, intertriginous inguinal tissues and on mucous membranes, especially in the vaginal area. These warts are sexually transmitted and may occur on the urethra, penile shaft, and rectum in males. Untreated lesions enlarge, developing cauliflower-like vegetation that can become quite large. They may remain for years and can be difficult to treat.

Treatment

Topical salicylic acid applied at home or cryotherapy at the physician's office are the most reliable and cost-effective treatments for common and plantar warts. Imiquimod may be a useful agent for facial lesions or for recalcitrant common warts. Injection of candida antigen (immune-modulation) intralesionally also appears to be an effective option. Pulsed dye laser therapy may be reserved for recalcitrant or hard to reach (periungual) warts [14]. Treatment options for condylomas include patient-applied therapies such as imiquimod and podofilox, along with cryotherapy and surgical excision [15].

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Hand-Foot-Mouth Disease

General Principles

Epidemiology Hand-foot-mouth disease (HFMD) is a contagious, usually benign, enterovirus disease caused mainly by Coxsackievirus A16 in the United States. It is most common in children, but can be seen in adults. HFMD is spread by contact with saliva, mucus, blister fluid, or fecal material from an infected person.

History and Physical Examination There may be a prodrome of malaise, loss of appetite, fever, and sore throat. One or two days later, tender aphthous sores appear in the mouth and a rash follows within 24 h. The self-limited rash is found especially on the palms and soles, but may occur on the face, buttocks, and legs. The skin lesions begin as small red macules, but develop into white 3–5 mm vesicles with a red periphery.

Treatment
Treatment of HFMD is supportive and symptomatic care. Cool fluids in small amounts help alleviate pain and swallowing in the eruptive phase. Infected patients should be kept at home until the rash clears and careful personal hygiene observed to prevent spread [16].

Fungal Infections and Yeast Infections

Dermatophytoses

General Principles
The group of dermatophytes includes fungi (tinea, ringworm) that are the most common fungal infections seen by primary care physicians. They survive in superficial keratin found on the skin, hair shafts, and nails. At times, they may be confused with eczema or other skin disorders.

Epidemiology Tinea capitis is most often seen in children, presenting as one or more round patchy areas of hair loss. These grow larger untreated and in some instances may cause an inflammatory reaction deeper into the scalp called a kerion. Kerions are boggy and indurated and can cause scarring alopecia. "Black dot tinea," the appearance of tinea in the scalp when the infected hair shaft breaks off at the scalp surface, is usually caused by *Trichophyton tonsurans*.

Diagnosis
Tinea barbae is a less common hair infection than tinea capitis. It may occur in those who work with or milk animals and thus lay their face on the side of the animal (such as dairy farmers). The hairs of a fungal-infected beard can be plucked painlessly and examined for hyphae. Tinea corporis and tinea faciei are common in children and adults. These are the classic "ringworm" appearing lesions, with the annular shape, clearing center, and a superficial active border. Untreated, they can achieve a large area with an irregular, serpentine border. In wrestlers, this form of infection is called tinea gladiatorum. Tinea cruris, or "jock itch," occurs mostly in adult males, and is more common in the warm summer months (Fig. 4). Like tinea pedis, this lesion can be extremely pruritic. Tinea pedis, also known as "athlete's foot," most classically presents in the toe web between the fourth and fifth toes in a young adult male, although any interdigital spaces can be affected. The warm, moist environment in the toe webs, the common

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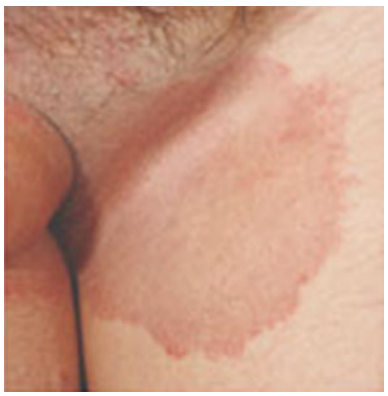

Fig. 4 Tinea cruris

exposure to locker room floors and communal baths, and the tightly fitting shoes over a sweating foot all combine to create this most common of tinea infections. Intense itching is most noticeable when the socks and shoes are removed. "Two feet-one hand" syndrome is occasionally noted, when both feet and the dominant hand the patient uses to scratch or pick at the infected site become infected [17]. Tinea incognito is the name given to any tinea infection which has been treated erroneously or inadvertently with topical steroids. The steroid blunts inflammation and disguises the usual active border. A careful history and review of medications will suggest the correct diagnosis, and KOH examination and culture will confirm the diagnosis.

Treatment

For small areas of infection, topical antifungal creams are effective and available over the counter. These should be continued for at least 1 week after apparent resolution to prevent recurrence. Larger areas are more efficiently treated with oral antifungals. For children, griseofulvin is the drug of choice [18]. In adults, fluconazole (Diflucan), itraconazole (Sporanox), or terbinafine (Lamisil) are recommended. In Athlete's Foot, treatment is aimed at drying the moist areas with cool Burrow's solution soaks and use of over-the-counter topical antifungal creams. In severe cases, oral antifungals can be used as for tinea corporis.

Prevention

Tinea gladiatorum in high school wrestlers can be prevented by use of prophylactic fluconazole [19].

Nail Infections

General Principles

Tinea unguium (onychomycosis) is an infection of the nails by dermatophytes, most often Trichophyton species. Patients may complain of discomfort walking due to the distorted nail and may suffer social embarrassment or loss of self-esteem from the cosmetic appearance [20].

Epidemiology The fungus may attack the nail proximally (less common, except in immune deficiency patients), distally (most commonly), or from a superficial surface invasion (white superficial onychomycosis) (Fig. 5).

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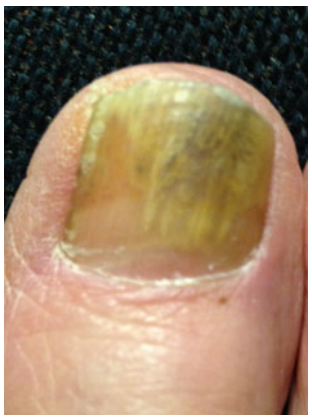

Fig. 5 Onychomycosis of nail plate beginning at the distal subungual area. Note characteristic streaks toward proximal nail matrix as channels

Diagnosis

Diagnosis can be made with KOH of subungual scrapings and histologic exam of distal nail clippings. Culture to confirm the species of fungus is desirable to guide treatment choices.

Treatment

Treatment of nail infections is more difficult than other tineas, requiring longer treatment intervals and accompanied by a higher failure rate. For toenails, terbinafine (Lamisil) given in a continuous dose of 250 mg/day for 12 weeks yields 70–88 % cure rate and is inexpensive in generic form. Pulse dosing at 500 mg/day 1 week per month for 3 months is less effective at 58.7 % cure rate [4]. Fingernails need be treated only 6 weeks at the same dose. Fluconazole and itraconazole have also been used with lesser success. For prolonged treatment options, baseline CBC and liver function tests with rechecks every 4–6 weeks are recommended.

Yeast

General Principles

Yeast organisms thrive in moist, warm environments, and infections are therefore most common in the interdigital spaces of those who work around water (dishwashers, cooks, bartenders) or in areas of the body where skin overlap provides warmth and moisture. These include the oral mucosa (especially in infants), the groin and genetalia, and inframammary or sub-pannus skin areas.

Epidemiology *Candida albicans* and other species of Candida live within the normal skin and mucous membrane flora, but cause infection with triggers such as pregnancy, oral contraceptives, topical or oral steroid use, oral antibiotics, diabetes, skin maceration, or any process interfering with cell-mediated immunity.

Thrush is oral candidiasis in infants or children. It is frequently seen in healthy newborns, where it may be asymptomatic or may cause some fussiness.

Diagnosis

Physical Examination Thrush in place of it appears as a creamy exudate or white adherent plaques from the accumulation of desquamated superficial epithelium. If removed, a raw, reddened tender epithelium is

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found. Candidal vulvovaginitis is a common infection in women, causing itching, burning, dysuria, and vaginal discharge. The vaginal tissues are red, swollen, and tender, and often a whitish curdy discharge is found. The vaginal pH is normal (pH < 4.5), distinguishing this discharge from other common causes of vaginitis. Candidal balanitis in the male presents with raw, red skin over the glans penis and skin of the shaft, especially in uncircumcised men. Candidal intertrigo is common, especially in warm climates and in obese or diabetic patients. Overlapping skin surfaces are ideal for monilial growth, and the resultant infection causes an area of bright red, superficially raw skin that is moist and confluent with peripheral "satellite" colonies. Candidal diaper rash causes red, raw, macerated, or fissuring skin in the diaper area of infants (or adults).

Treatment

Thrush is treated in children with nystatin oral suspension. In adults this is most efficiently accomplished by oral fluconazole. For patients with cancer or HIV, prophylactic dosing can help prevent relapses. Treatment of vulvovaginitis with oral fluconazole (150 mg PO, one dose only) is usually effective. Alternatively, vaginal and intravaginal creams and troches are available (terconazole and miconazole). As in the female, a single oral dose of fluconazole 150 mg is as effective as topical antifungal creams applied daily for 7 days (clotrimazole and miconazole) for treatment of balanitis in the male. Treatment of intertrigo is aimed at removing the moist environment using Domeboro's solution for soaks several times a day and at eliminating the actively growing yeast with antifungal creams. For candida diaper rash, excess moisture can be addressed by frequent diaper changes or intervals of open-air exposure without a diaper. Antifungal creams are applied twice daily for 7–10 days. Avoidance of formulations containing both antifungal and steroid creams is usually prudent, as the steroid component may cause prolonged duration of the moniliasis [4].

Tinea Versicolor

General Principles

Tinea versicolor is a commonly encountered infection of the skin, whose name originates from the fact that the affected skin has a different color in the summer than in the winter.

Epidemiology It is caused by dimorphic lipophilic yeast, *Pityrosporum ovale* and *Pityrosporum orbiculare*, together previously called *Malassezia furfur*, that thrives best in the stratum corneum and hair follicles of sebaceous-rich skin.

Diagnosis

History and Physical Exam The characteristic appearance of the rash is an area of cape-like confluence, usually over the shoulders and upper chest, with a reticular border of multiple oval macules of varying size. In the winter months, Caucasians will be found to have a slightly scaly, light brown rash; in the summer, the same individual will present with white oval to circular patches that stand out against the tanned skin – hence the name "versicolor." While the upper chest is most often involved, the rash may extend to the upper arms, neck, and abdomen. The rash may be slightly itchy, but is usually asymptomatic.

Laboratory The clinical diagnosis can be confirmed by lightly scraping the lesions with a #15 knife blade, producing a powdery scale (Fig. 6). A potassium-hydroxide preparation of the scale will demonstrate the classic "meatball and spaghetti" appearance of the hyphae and spores.

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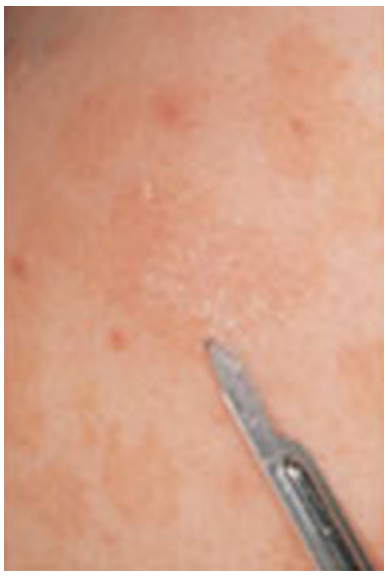

Fig. 6 Powdery scale noted on scraping with #15 knife blade. KOH shows "meatballs & spaghetti"

Treatment

For limited disease, topical antifungals, such as ketoconazole 2 %, are highly effective and still the treatment of choice. For extensive rashes or failures of topical treatments, oral antifungals of the azole class have proven to be effective.

Infestations

Lice/Pediculosis

General Principles

Lice are obligate human ectoparasites that feed by piercing the skin with their claws and ingesting the blood, causing an itchy reaction in the skin of the patient. They live at the border of skin and hair and are visible as a 1–2-mm mobile insect. Females lay 0.8-mm eggs (nits) that are glued firmly to the hair shaft. After an 8–10 day incubation, the larvae hatch and mature. Live nits will be found within the first ¼ inch of a growing hair, but empty nits will remain attached to hairs for months.

Epidemiology There are three main species of lice: *Pediculosis capitis* or head lice, *Pediculosis corporis* or body lice, and *Pthirus pubis* or pubic lice. Pubic lice are the most contagious of sexually transmitted diseases, with a 90 % chance of acquisition with only one exposure. Head lice are most commonly seen in school children and are the focus of greatest attention by parents, school nurses, and physicians.

Diagnosis

The diagnosis is made by demonstrating lice or by combing the hair with a fine-toothed "nit comb."

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Treatment

Growing resistance of lice has occurred to the most commonly used chemicals, permethrin 1 % (Nix) and pyrethrins 0.3 % and piperonyl butoxide 4 % shampoo (RID). These over-the-counter preparations are now often effective in only about 45 % of patients. Permethrin is considered the first choice, can be used in patients 2 months and older, and is least expensive. Malathion (Ovide) 0.5 % lotion is used in treatment failures but is much more expensive and cannot be used in children under 6 years of age [21]. Parents uneasy with insecticide use can utilize the nonpharmacologic techniques of wet-combing or application of Cetaphil in a dry-on suffocation-based treatment plan. While questions have been raised about study design, Pearlman reported a 95 % eradication rate in patients who had failed other treatments using this simple and inexpensive technique [22]. Treatment for body and pubic lice is similar. Ivermectin (Stromectol) 200 mcg/kg orally with a second dose repeated in 10 days is also effective for all types of lice and can be used on patients $\geq$ 15 kg at a cost of approximately $10–$30 per dosage [23].

Scabies

General Principles

Scabies is an intensely pruritic infestation caused by the mite *Sarcoptes scabiei*. It is the most common of infestations and is highly contagious. Close personal contact, as within households or nursing homes, will result in rapid spread. The initial symptoms begin insidiously with one or two mildly itchy sites. The fertilized female mite burrows into the stratum corneum and, through her 30-day life cycle, continues to burrow up to several centimeters. Along the way, she leaves a path strewn with eggs (at a rate of 1–3 per day) and fecal pellets (scybala). The eggs hatch and the larvae mature within 2 weeks. The adult forms mate, and the cycle is repeated. Meanwhile, the discarded scybala and egg casings prompt an extremely pruritic allergic rash at the sites of infestation. The deceptively slow start of the disease, lasting up to a month, is rapidly replaced by a widespread, intensely itching rash as the mites multiply exponentially causing papules, vesicles, and burrows.

Diagnosis

The diagnosis can be confirmed by scraping a burrow and finding egg casings, eggs, scybala, or mites (Fig. 7). Mites are less frequently seen in the usual cases of scabies. Only in crusted (Norwegian) scabies

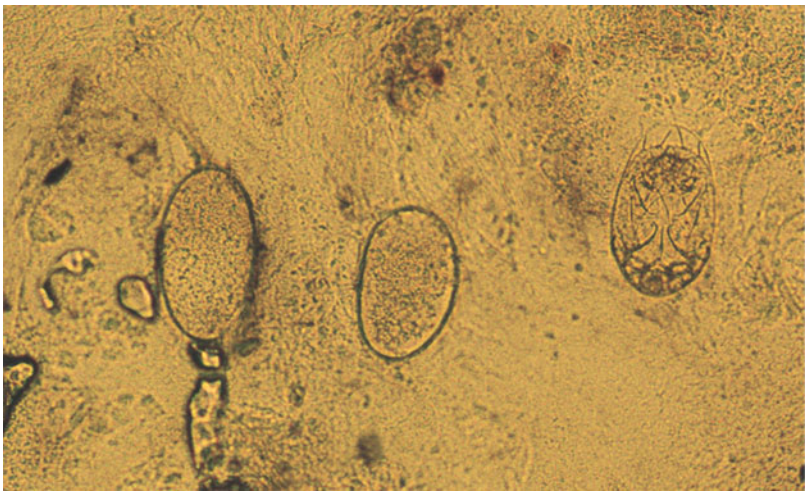

Fig. 7 *Sarcoptes scabiei*, wet mount of KOH prep

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are there hundreds or thousands of mites. It is an uncommon form and is found in patients with immune deficiencies, mental disorders, or the elderly.

Physical Examination Sites of infestation are classically the hands, feet, wrists, axilla, waistline/abdomen, and genetalia. Infants and children may have greater number on the palms and soles. Nocturnal itching is classic, and if left untreated, the infestation can last for years.

Treatment

Scabies is treated with permethrin 5 % (Elimite) cream, the drug of choice. All members of the household should be treated, regardless of symptom presence. One application is considered curative, although many practitioners repeat the treatment in 1 week. Oral Ivermectin (Stromectol) is another first-line treatment option. It is usually chosen for treatment failures, the elderly, or those unable to complete topical therapy. Treatment for crusted scabies requires dual regimens of topical permethrin and oral Ivermectin as well as special environmental measures [21].

Patient Education All clothing and personal items should be washed in hot water and dried in a hot dryer. It is important to inform patients that itching usually improves shortly after treatment, but persists for 3–4 weeks thereafter.

Chiggers

General Principles

Chiggers, also known as the harvest mite or red bug, are bites from the barely visible Trombicula mites causing an irritating and very itchy rash.

Diagnosis

History and Physical Examination Bite sites are most often near the ankles and legs, but can occur in skinfolds, especially in the groin, axilla, or waistline. The itching is most severe for the first 1–2 days and resolves spontaneously in 1–2 weeks afterwards.

Prevention

Bites can be prevented by use of proper clothing and any DEET-containing repellants.

Delusional Parasitosis

General Principles

Delusional parasitosis is a psychodermatologic condition in which the patient is firmly convinced of an infestation with some type of organism and uses destructive measures (scratching, gouging, shaving) on the skin to combat the problem. The condition may last for years, and others within the patient's orbit (spouse, child) may also become convinced of its existence (termed *folie à deux*).

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Diagnosis

History and Physical Examination The patient classically presents to their PCP with symptoms of a crawling or itchy sensation for months or years. They usually bring with them "evidence" of the infestation, called the "matchbox sign," in which pieces of skin and debris they have removed are placed in tissue paper and placed in a container, such as a matchbox or plastic baggies. Skin exam reveals numerous active and healing excoriations in reachable anatomic sites and no lesions in unreachable areas.

Treatment

Treatment requires the investment of time to listen attentively and empathetically to the patient's complaint to establish rapport. A systematic evaluation is required to ensure there really is no infestation. Often the symptoms persist, and the use of low-dose atypical antipsychotic medications is required for resolution [24].

Referrals Referral to psychiatry may be a useful adjunct, but the patients often refuse the referral as unnecessary and an implication of the physician's lack of belief in their symptoms and needs.

Cat Scratch Disease (CSD)

General Principles

Cat scratch disease is an illness caused by *Bartonella henselae* and characterized by unilateral adenopathy, malaise, anorexia, aches, and a moderate to low-grade fever. It is most often seen in children, but can be present in adults. It is usually a benign, self-limited disease, although rarely it can cause ophthalmic complications or neurologic symptoms. Over 90 % of patients have a history of contact with a cat or kitten. The bacteria is passed from pet to owner by scratches or bites.

Diagnosis

The diagnosis of cat scratch disease can be confirmed by the combination of a history of exposure to cats, lymphadenopathy, and elevated antibodies to *B. henselae*.

Physical Examination A red papule or vesicle is often found on the hand, which, in contrast to insect bites, is non-pruritic. As the vesicle heals, regional adenopathy (usually ipsilateral) occurs. Persistent lymphadenopathy, which is often the presenting symptom, usually resolves in 1–6 months.

Treatment

Treatment is usually unnecessary [4].

Bedbugs

General Principles

Bedbugs (*Cimex lectularius*) are small, light-aversive insects that hide near beds and obtain blood meals from humans while they sleep. They are found worldwide and have undergone a significant resurgence in the past decade, most likely due to expanded travel and increasing resistance to current insecticides. Cimex saliva, which incites the post-bite rash and evokes a wide variety of responses from their victims, is injected into the skin at the bite site. The host reaction is usually an intensely pruritic maculopapular rash, although papules, wheals, and vesicles have been reported.

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Diagnosis

Confirmation requires a careful examination of the sleeping premises. Molted exoskeletons, dark granular feces, eggs, and debris all can be found within a few feet of the sleeper. These sites are often in mattress seams, headboards, wall hangings, peeling wallpaper, or other similar sites [25].

Physical Examination Bite sites are found on exposed skin. The classic linear three-bite presentation, "breakfast, lunch, and dinner," should suggest the diagnosis of bedbugs.

Treatment

Bite treatment is aimed at relief of the itching with topical steroids or oral antihistamines. The rash is self-limited, resolving in 1–2 weeks.

Patient Education Eradication of an infested site can be frustrating and costly. An integrated pest management strategy is recommended by the Centers of Disease Control and Prevention (CDC) as well as the Environmental Protection Agency (EPA) to eliminate infested sites. The EPA and CDC have web sites with features that answer frequently asked questions (FAQs) as well as information on the life cycle of the insects and methods of control.

Myiasis (Botfly)

General Principles

Cutaneous myiasis (botfly infestation) occurs when eggs of a human botfly, *Dermatobia hominis*, are deposited into the skin of the host. The botfly itself does not bite, but uses other biting insects to transmit its eggs by a process called phoresis. Infestation is most commonly seen in late summer or fall, frequently in travelers who have visited Central or South America.

Diagnosis

History and Physical Examination Clinically, the patient presents with a red papule that can appear on any exposed skin surface. As the larvae grows in the subcutaneous tissue, an air vent into the skin is created and the larvae rise up every minute or so for oxygen, causing a sensation of movement within the skin.

Treatment

Treatment consists of recognition of the condition and removal of the larvae [4].

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Family Medicine
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Skin Tumors

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General Principles

Skin tumors encompass both benign and malignant entities; some tumors will self-resolve, while others may require treatment. Currently there is no overwhelming recommendation for universal screening for skin cancer. The United States Preventive Services Task Force (USPSTF) [1] concludes that "the current evidence is insufficient to assess the balance of benefits and harms of using a full body skin exam by a primary care clinician or patient self examination for the early detection of cutaneous melanoma, basal cell cancer, or squamous cell skin cancer in the adult general population." Grade I. The USPSTF was unable to detect any harm of screening. Many physicians perform a skin exam during the regular physical examination, and others will ask patients if there has been a history of a mole change or other skin concerns and tailor their exam to the patient's history. The patients most likely to benefit from screening are those that would be considered high risk. High-risk patients tend to be fair-skinned individuals over age 65, patients with atypical moles, and patients with more than 50 moles, personal history of excessive sun exposure, tanning bed use, or skin cancer in the family. Most screening is aimed at early detection of melanoma as early detection can alter the course of the disease.

Approach to the Patient

History

The important aspects of history include duration of the lesion, change in appearance, symptoms, and history of trauma. Patients' pertinent past medical history may include history of sun exposure, medications (including immunosuppressives), and family history of certain skin tumors.

Physical Examination

The physical examination should include observation for all characteristics of a lesion. Pigment components can range from tan to brown to black. Vascular characteristics may include different shades of red, purple, or black, the shape of the blood vessels (such as branched atypical vessels in basal cell carcinomas), and the ability of the lesion to blanch with pressure. Skin tumors can differ by location of the lesion in relation to the epidermis such as it is atop the skin (seborrheic keratosis), within the skin (junctional nevus), or under the skin (lipoma). Furthermore, some skin tumors are more common in damaged skin, and examining the surrounding skin for sun damage or scarring is an important aspect of the exam. Using a dermoscope to further elucidate surface characteristics such as vascular formations and pigment distribution can be very helpful in diagnosing skin tumors. In some cases photographing a low-risk skin lesion and providing surveillance can be helpful.

Biopsying a skin tumor may be necessary to determine diagnosis, while at other times diagnosis may be obvious with a good physical examination. Alternatively patients may request removal or biopsy for

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reassurance or cosmetic reasons. Referral may be the wise choice in lesions that are difficult to diagnose or when biopsy may require specialized skills like Mohs surgery.

Keratosis

Seborrheic Keratosis (SK)

General Principles

Definition SKs occur as a focal proliferation of epidermal cells; there can be varying amounts of hyperpigmentation, and keratinocytes secrete substances that increase pigmentation (Fig. 1). Leser-Trelat sign [2] is when a patient develops numerous SKs suddenly; it is associated with internal malignancy such as carcinoma of the GI tract.

Epidemiology SKs are commonly found only in patients over 30, equally in male and female patients. Incidence increases with older age.

Classification Irritated SK is a variant that appears redder and histologically looks irritated.

Diagnosis

History Most patients will describe a slow-growing lesion that has become progressively larger and darker over time. Some patients record being able to scratch it off but it will recur. They typically cause no symptoms; however, they can become irritated by friction.

Physical Examination SKs are 4 mm to 2 cm oval lesions, and color can range from pink to the more common tan and dark brown. They typically appear as rough and dry stuck-on lesion on the top of the skin. Commonly they have a waxy or oily feel. Patients may have multiple lesions especially on the chest and back. Inflamed lesions can have a redder color. When examined with a dermoscope, the surface characteristics of retained keratin cysts can be seen that look like milia and comedo-like openings or a cerebriform (brainlike) appearance [3].

Special Testing Atypical SKs should be removed by shave or elliptical excision. On occasion biopsy may be necessary for lesions that appear irritated or scabbed.

Differential Diagnosis Solar lentigo, malignant melanoma, squamous cell carcinoma, pigmented actinic keratosis, and pityriasis rosea.

Treatment

Therapy is generally not needed for most lesions, and reassurance is typically adequate. Cryosurgery can be used for shallow lesions but may result in hypopigmentation. For patients who want them removed, a shave biopsy, cautery, or curettage can be done but may result in scarring.

Referrals Dermatology consultation can be useful for patients who want extensive treatment.

Counseling Patients who request treatment should be warned of possible hypopigmentation or scarring.

Patient Education Reassurance can help patients understand that these are benign lesions, but they will likely remain or may grow.

Sunscreen should be recommended to prevent further skin damage.

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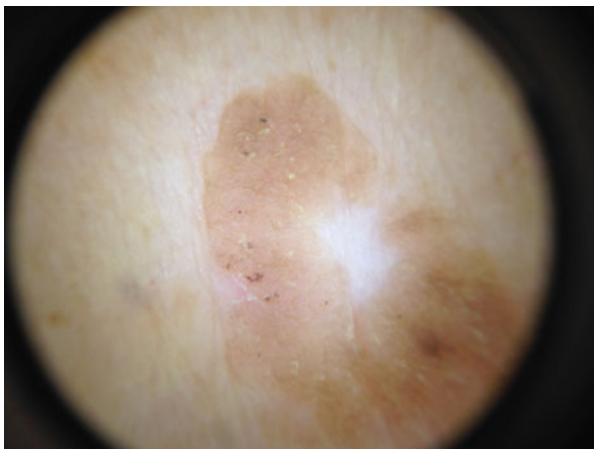

Fig. 1 Early seborrheic keratosis with typical stuck-on appearance and developing milia and comedo-like openings commonly seen under dermoscopy

Actinic Keratosis (AK) aka Solar Keratosis

General Principles

Definition Actinic keratosis are very common nonpigmented lesions (Fig. 2). They consist of atypical keratinocytes that have partially invaded the epidermis. AKs occur after repeated or prolonged sun exposure in susceptible patients leading to skin damage and inability for the body to repair. They are considered premalignant as some may develop into squamous cell carcinoma (SCC) at a rate of 6 % over a 10-year duration [4].

Epidemiology AKs occur in patients over the age of 40, more common in males and patients with fair skin and outdoor occupations. Seventy-five percent of people over 80 are affected. They can develop in younger patients who get a lot of sun exposure.

Approach to the Patient

Diagnosis

History Patients will complain of a red or scaly spot that has been present for months to years. They often will pick or attempt to scratch it off, but it will always reform. Rarely they will cause pruritus or burning.

Physical Examination Lesions are typically found in sun-damaged skin or areas of sun exposure. AKs are generally 3–10 mm in size and may be red or yellow in color with an adherent scale. They will feel rough to the touch. Commonly affected areas are the face, ears, scalp, neck, forearms, and hands.

Special Testing Biopsy should be done in thicker lesions when the diagnosis is unclear and SCC is in the differential.

Differential Diagnosis SCC, seborrheic keratosis, eczema, basal cell carcinoma.

Treatment

Therapy is usually recommended to prevent progression to SCC [5].

Cryotherapy applied for 5–10 s will cure over 75 % of lesions. Surgical curettage and electrodesiccation are more effective for thicker lesions.

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Medications

Topical fluorouracil (5FU) 5 % cream is applied twice daily for 2–4 weeks. Patients will experience local irritation at the site during treatment [5]. Topical imiquimod 5 % cream is applied once daily up to three times a week for 16 weeks and will also cause local irritation. Topical diclofenac applied twice daily for three months is effective in approximately 50 % of subjects but is limited by local side effects. Chemical peels are also effective.

Photodynamic therapy with sensitizing agents is also effective.

Referrals Dermatology consultation may be needed in extensive cases.

Counseling Patients should be counseled that hypopigmentation, scarring, and hair loss may occur with cryotherapy. Topical therapies may have a lot of irritating side effects during treatment.

Patient Education Patients should be advised to protect themselves from the sun through clothing and sunscreen. Regular skin exams should be performed as patients with AKs may be more likely to get other types of skin cancer.

Pigmented Lesions

Nevus (Common Mole)

General Principles

Definition A nevus is a confined nest of melanocytes within the skin.

Epidemiology Nevi are acquired in childhood and young adulthood, and new moles that develop in later adulthood should be viewed with caution.

Classification

Dermal/Intradermal A nevus that is raised above the epidermis; it may be flesh colored or pigmented.

Junctional A nevus with cells at the dermoepidermal junction.

Compound A nevus with raised pigmented cells in the dermis and dermoepidermal junctions.

Dysplastic (Clark's Nevus) Nevi that are irregular-appearing moles with an uneven distribution of melanocytes giving them a nonuniform appearance. Histologically they are compound nevi with

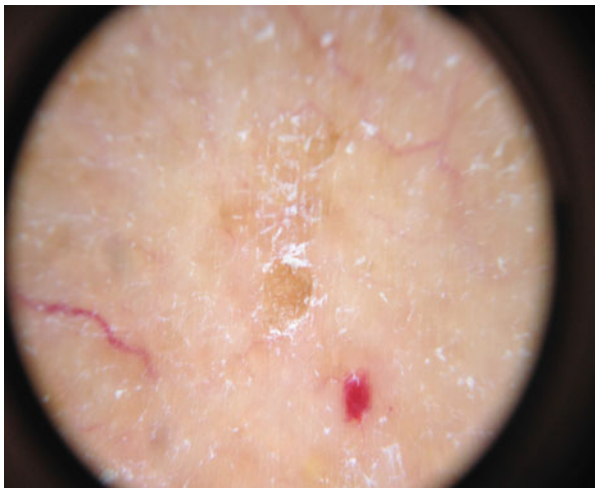

Fig. 2 Actinic keratosis seen centrally through polarized dermoscopy; the surrounding skin is sun damaged and cherry angioma also visible at 5 o'clock

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Table 1 Three-point checklist – dermoscopy

Nevus	Melanoma
Regular pigment network	Irregular pigment network
Symmetry of color/structure	Asymmetry of color or structure
No blue or white coloring	Blue or white coloring

melanocytes that are irregularly distributed. The familial atypical mole and melanoma syndrome (FAMM) [4] is a condition occurring in patients with many nevi – some atypical – and first or second degree relative with melanoma; FAMM vastly increases a patient's risk of developing melanoma.

Congenital Nevus A mole that is present at birth and may be very large. There is a small increased risk of melanoma especially in larger or nonuniform lesions (Fig. 3).

Blue A nevus having a blue or black appearance as the melanocytes are concentrated deep in the dermis.

Halo Nevi A growing nevus surrounded by an area of hypopigmentation which is an inflammatory response. They are typically found in adolescents and the halo resolves with time.

Spitz Nevus/Spindle Cell Nevus A reddish papule found in children; development in adults is a concern for melanoma.

Nevus Spilus A group of speckled darker brown spots within a larger tan/brown macule.

Approach to the Patient

Diagnosis

History The physician should inquire about any recent changes in moles. Sun exposure history and family history of melanoma should be asked.

Physical Examination Nevi can be quite variable in appearance. Color can vary from flesh colored to pink, tan, dark brown, blue, or black.

The physician should visually inspect the skin to see if there is a regular identifiable pattern that defines one of the benign nevus types. In addition many patients have similar characteristics to their moles and a different-looking mole commonly termed the "ugly duckling" should raise suspicion. Dermoscopy is helpful in reassuring the patient that the skin lesion looks very regular. The three-point checklist [3] can help the physician determine if a lesion is more likely to be a nevus versus a melanoma (Table 1).

If 2 of 3 or 3 of 3 melanoma criteria are present, the physician should biopsy the lesion.

Special Testing A biopsy should be performed on any suspicious lesion. Shave biopsy is acceptable in a low-risk thin lesion or likely dermal nevus. Excisional biopsy is recommended if melanoma is in the differential.

Differential Diagnosis Melanoma, seborrheic keratosis, solar lentigo.

Treatment

Therapy typically consists of observation and reassurance. Patients may request removal due to recurrent irritation (dermal nevi) or for cosmetic reasons. Depending on the type of nevus, biopsy methods will differ. A shave biopsy may be useful for a dermal nevus that is growing above the skin surface or for a thin nevi. Punch biopsy is appropriate for small lesions 5 mm or less.

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Behavioral

Medications Prescription and over-the-counter creams are not indicated nor effective in removing nevi.

Referrals Dermatology consultation is indicated for very large nevi or patients that may have multiple dysplastic nevi or suspicious nevi that the physician may feel uncomfortable biopsying.

Counseling Patients should be warned that removal may result in scarring or keloid formation in susceptible patients.

Patient Education and Activation Patients should be reminded to protect their skin with sunscreen and clothing. Moles that are changing or bleeding should be brought to the attention of the physician; the ABCDE rules [6] are a good guide:

ABCDE

(A) **Asymmetry**
(B) **Border irregularity**
(C) **Multiple colors**
(D) **Diameter greater than 5 mm/quarter inch**
(E) **Evolving – change in size, shape, or color**

Solar Lentigo/Actinic Lentigo (Liver Spot)

General Principles

Definition Lentigines are acquired pigmented skin lesions caused by sun damage. They are commonly found on sun-exposed areas such as the face, neck, and extremities [4]. Histologically there is an increase in melanocytes and keratinocyte hyperpigmentation [2]. They are considered an adult variant of the freckle. However, they do have the capacity to change and undergo malignant transformation to the melanoma form lentigo maligna melanoma.

Epidemiology Lentigines typically occur in patients over the age of 40 and are more common in Caucasians who have had significant sun exposure and on sun-exposed areas.

Classification

Inkpot Lentigo Uniformly dark black-pigmented lesion with irregularly dispersed pigment.

Peutz-Jeghers Syndrome Multiple mucus membrane lentigines – associated with intestinal polyps.

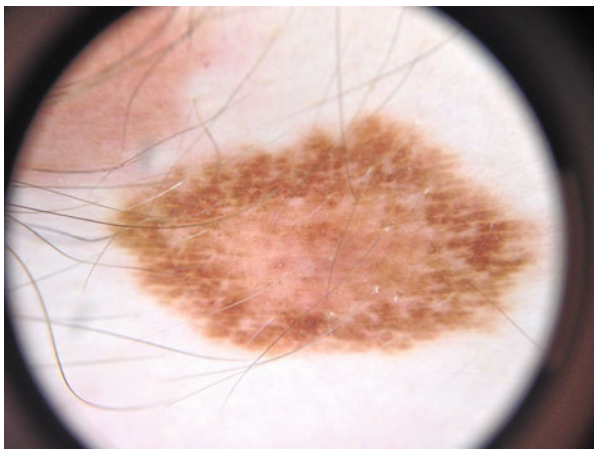

Fig. 3 This congenital nevus in a 45-year-old male measured 2 cm and had never changed

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Lentigo Maligna (LM) It is the in situ malignant variant – a lentigo that has transformed to a superficial spreading melanoma/melanoma in situ.

Approach to the Patient

Diagnosis

History Most patients will report noticing brown spots on sun-exposed areas; the spot becomes darker upon sun exposure and may lighten during the winter months. Patients typically report developing more of the spots as they age.

Physical Examination The physician will see a tan to dark brown to black blotchy macule ranging in size from 2 to 20 mm. Common affected areas are the sites of most frequent sun exposure: the back, face, lips, dorsum of hands and forearms, and anterior legs in women. Dermoscopy can be helpful to see if the pigment is evenly distributed within a lesion or abnormally concentrated which can be a sign of developing malignancy [3].

Special Testing Biopsy should be performed on a lesion that is changing or has a large variation in color. Punch biopsy can be performed in an irregular area of large lesions, while elliptical excision is desirable when possible.

Differential Diagnosis Melanoma, nevi, lentigo maligna, lentigo maligna melanoma, pigmented actinic keratosis, flat seborrheic keratosis.

Treatment

Cryotherapy may be done on small lesions; it works variably and can lead to hypopigmentation.

Medications Treatment is not necessary, but if desired, medications to bleach the skin can be used but typically take many weeks to work. Hydroquinone 4 % cream bid, azelaic acid 20 % cream bid for 2–4 weeks, and glycolic acid peels are all somewhat effective.

Referrals Dermatology consultation may be warranted in lesions that are undergoing rapid change or have very irregular borders that the physician does not feel comfortable biopsying.

Counseling Patients should be warned that some treatments may result in uneven bleaching or thus skin or temporary irritation.

Patient Education and Activation Patients should observe lesions for change. Sunscreen, hats, clothing, and sun avoidance can prevent lentigines from forming.

Malignant Skin Lesions

Melanoma

General Principles

Definition Melanoma is the type of skin cancer characterized by irregular melanocytes growing in an irregular pattern. Melanomas may arise in preexisting nevi or arise de novo. They can spread locally through lymphatic extension or by hematogenous dissemination to the lungs, liver, and other organs.

Epidemiology Melanomas account for but cause 5 % of skin cancers and most skin cancer deaths. Its incidence is increasing with 76,000 new cases per year with almost 10,000 deaths per year [7]. Most cases are in elderly males; however, it is the most common cancer in young adults. There is a slight female predominance in superficial spreading types and lentigo maligna melanoma in elderly patients. In males the most commonly affected areas are the trunk, head, and neck and in females the extremities.

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Classification

Superficial Spreading The most common type; the melanoma is slowly growing horizontally usually originating from a preexisting nevus.

Nodular They are raised brown/black rapidly growing lesions, often with red elements and hemorrhage or ulceration.

Lentigo Maligna Melanoma A thin horizontally spreading lesion arising from a lentigo in a sun-exposed area.

Acral Melanoma A palmar or sole melanoma more common in African Americans and Asians.

Nail Melanoma A rare type of melanoma arising from the nail matrix causing an irregularly pigmented streak in the nail.

Amelanotic Melanoma A nonpigmented melanoma, these should be suspected in a growing lesion that is not easily identifiable as another type of skin lesion (i.e., dermatofibroma); the common saying is "if it's pink stop and think."

Approach to the Patient

Diagnosis History The patient may note that a lesion has changed in appearance over time. Symptoms may include itching, scabbing, or bleeding. Medical history may include certain risk factors such as advanced age, sun exposure, sunburns at young age, pale pigmentation, sun-tanning bed use, immunosuppression, multiple nevi, atypical nevi, or family history of melanoma.

Physical Examination Melanomas usually have visible discoloration, multiple colors, uneven pigment, or ulceration. Areas of uneven pigment can include darker black coloring or loss of coloring (regression). Dermoscopy can be a valuable tool for assisting the physician and differentiating between nevi and melanoma by magnifying the lesion further revealing pigment pattern characteristics, asymmetry, and recession. Area lymph nodes should be palpated when melanoma is suspected.

Laboratory and Imaging Ancillary testing is generally not recommended unless the tumor has metastasized in which case chest x-ray (CXR) and CT scan may help with staging.

Special Testing Suspected melanoma should be biopsied preferably with an excisional biopsy typically with 2–4 mm margins. On extremities the biopsy should be oriented along the longitudinal axis. Lesions suspicious for nail melanoma should include the nail matrix and may be best left to a physician with experience in biopsying the nail bed. Deep shave biopsy may be acceptable in cases where there is a low suspicion for melanoma, and complete removal will take place with the shave, e.g., a thin lesion. A punch biopsy may be acceptable in cases where the entire lesion cannot be removed, rapid diagnosis is needed, or in a sensitive area such as in facial or acral locations. In case a large partial biopsy is necessary, it should be performed on the most atypical portion of the lesion, and the physician should understand that there will not be reliable depth reporting from the biopsy report.

Pathology guides treatment and further workup [7, 8]. Staging depends upon several characteristics of the lesion. The Breslow maximum tumor thickness measures how deep the malignant cells invade the dermis. The mitotic rate – mitoses per mm squared – and presence or absence of ulceration are all reported in the pathology report and are important prognostic indicators. The Clark level of anatomic invasion and microsatellite tumor is also important. Sentinel node biopsy is often recommended for melanomas greater than 1 mm thickness and its results may determine prognosis.

Differential Diagnosis Nevi, dysplastic nevi, seborrheic keratosis, solar lentigo, inflamed SK, pyogenic granuloma, pigmented BCC, dermatofibroma, hemangioma.

Treatment Therapy after biopsy usually includes further excision; it is guided by tumor thickness (Table 2).

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Table 2 Breslow thickness and re-excision margin

	Breslow depth	Re-excision margin
Melanoma in situ	Only involving epidermis	0.5 cm
Melanoma	<1.0 mm	1 cm
Melanoma	1.01–2.0 mm	1–2 cm
Melanoma	>2.0 mm	2 cm

Medications Melanoma vaccines have been developed and may be used by oncologists as adjuvant therapy.

Referrals Consultation with a dermatologist or oncologist who treats malignant melanoma is recommended, especially if such treatments with interferon and other immunotherapy are considered.

Lentigo maligna melanoma lesions can be difficult to excise in total due to their large size, so off-label treatments such as topical imiquimod and radiation therapy are often employed by specialists.

Counseling Prior to biopsy and re-excision, patients should be warned of the possibilities of poor healing and scarring as well as the possibility of incomplete removal.

Patient Education Patients should be reminded to assess skin lesions for change and schedule regular skin exams. They should be encouraged to limit sun exposure and protect themselves with the use of sunscreen and clothing.

Basal Cell Carcinoma

General Principles

Definition Basal cell carcinoma (BCC) is the most common type of skin cancer. It originates in the keratinocytes of the basal layer of the epidermis. It can locally invade but rarely metastasizes.

Epidemiology BCC occurs in older patients typically on sun-exposed skin, more commonly in Caucasians with fair skin.

Classification

Nodular These are the most common and can be pigmented or nonpigmented.

Superficial BCC These are oval thin flat scaling lesions.

Sclerotic/Morpheaform These are rare and appear flat/scar-like and can be difficult to treat.

Approach to the Patient

Diagnosis

History Most patients will report a slowly growing lesion that may ulcerate or scab.

Physical Examination BCCs are commonly pink or white pearly nodules 3 mm to 1 cm in size, with crusting or bleeding. They are most frequently on sun-exposed areas such as the head and neck. The surrounding skin typically shows evidence of chronic sun exposure. Dermoscopy can be useful in identifying BCC as commonly one will see branching blood vessels on the surface (Fig. 4).

Special Testing Biopsy through an excisional or shave biopsy is needed for diagnosis. For excisional biopsy 1–3 mm margins are preferred in areas where there's sufficient skin to close the wound. Shave biopsy may be necessary on areas of the face or scalp where skin preservation is important. However, if performing a shave biopsy, the physician must prepare the patient that if the pathology returns as a BCC another procedure may be necessary.

Treatment If the lesion is excised in total, no further treatment is necessary [9]. Curettage and electrodessication can be performed on incompletely removed BCC. Mohs surgery is a treatment typically

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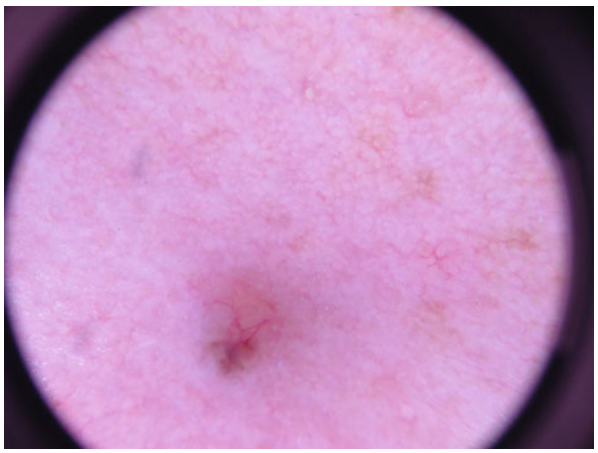

Fig. 4 Pigmented BCC under dermoscopy; branched vessels and irregular blotches of pigment seen

done at a specialist's office where successive layers of tumor are removed then immediately examined under the microscope until the last layer is free of all tumors. The procedure may be necessary in cosmetically sensitive areas such as the face or when tumors have recurred in the same area. Mohs is expensive and time consuming and may not be available in all areas. Surveillance for all removed BCCs should be performed as 5 % of treated lesions will recur.

Radiation therapy may be done in difficult-to-treat lesions such as large extensive lesions or as a palliative treatment when surgery is unlikely to occur. Photodynamic therapy can also be used in which topical photosensitizing agents are applied to the tumor followed by light therapy.

Cryotherapy has been used to treat very thin lesions.

Medications 5FU can be used to treat superficial BCCs; it causes an inflammatory response which destroys the BCC.

Imiquimod (Aldara) 5 % applied daily for 6 weeks can be used to treat superficial BCC. It causes severe inflammation which in turn destroys the BCC.

Counseling Patients should be counseled that biopsy may result in scarring and there is a small change of recurrence even with complete removal.

Patient Education Patients should be advised to protect themselves from the sun with sunscreen, UV-obstructing clothing, and hats.

Squamous Cell Carcinoma (SCC)

General Principles

Definition Squamous cell cancer is a skin cancer that arises when atypical keratinocytes invade the epidermis [10]. Most SCCs are highly curable with appropriate treatment, but certain types have a predilection to metastasize through lymph channels [11]. The rate of metastasis is 2–6 % [10].

Epidemiology SCC tends to occur in Caucasians with fair skin and occur on the face, neck, head, and hands. SCCs are also common in transplant patients who are on immunosuppressants. They tend to develop in areas of preexisting damage to the skin from sun, radiation, arsenic, burns, scars, and presence of the HPV [12]. Actinic keratoses are the precursors of SCC where the atypical keratinocytes have partially invaded the epidermis.

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Classification

Bowen's Disease SCC in situ that has not invaded past the epidermis.

Keratoacanthoma These are a low-grade variant of SCC that develop suddenly and have a central core of keratin.

Oral SCC It is a more aggressive type of SCC.

Erythroplasia of Queyrat Penile SCC It often appears ulcerated and is related to the HPV virus.

Vulvar SCC Vulvar SCC is a variant that arises from the HPV virus. It is more common in immunocompromised hosts.

Approach to the Patient

Diagnosis History Most patients will report a nonhealing scab or flaky area of several months or more duration.

Physical Examination Most lesions will appear as a thin pink plaque or nodule with an adherent scale. The surrounding skin will often show sun damage. The nearby area and lymph nodes should also be examined.

Laboratory and Imaging CT of the area may be necessary to image lymph nodes in high-risk lesions such as oral SCC.

Special Testing An excisional biopsy of the lesion with a 4 mm margin is the gold standard as the specimen can be assessed for complete removal of the cancer. This can be accomplished during the original excisional biopsy. High-risk SCCs may have microscopic spread and Mohs surgery may need to be performed to assess for invasion.

Differential Diagnosis Actinic keratosis, superficial BCC, lichen planus.

Treatment Therapy for small well-defined SCC is complete with the original excisional biopsy if pathology reveals clear margins. High-risk SCCs may have microscopic spread, and Mohs surgery may need to be performed to assess for invasion [12]. If a low-risk SCC extends to the margin of a biopsy specimen, a repeat excision or curettage + electrodessication must be performed.

Mohs surgery is indicated for high-risk lesions or SCC that would be difficult to remove completely by traditional surgical excision. Mohs is ideal for difficult-to-treat areas, such as the eyes, lips, nose, and ears.

Curettage and electrodessication alone can be used to remove small well-defined SCCs less than 1 cm in size.

Cryosurgery can also be used for small well-defined low-risk tumors by experienced physicians; it is not acceptable for high-risk or recurrent tumors.

Radiation treatment is used to decrease tumor size in areas where resecting the lesion would be technically difficult. Cosmetic problems such as telangiectasia can occur, so it is not recommended in younger patients.

Photodynamic therapy is under investigation as a potential treatment.

Medications 5FU is being tested for treatment of superficial SCC.

Referrals Dermatology consultation is prudent for high-risk lesions, large lesions, or those requiring Mohs surgery.

Counseling Patients should be advised of scar potential prior to removal of tumor.

Patient education Patients should be advised that SCCs may recur, and they should have follow-up exams. Sun avoidance and protection with sunscreen and clothing should be done.

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Keratoacanthoma

General Principles

Definition Keratoacanthomas are thought to be variants of squamous cell carcinoma that arise from the hair follicle of the skin. They are made up of atypical keratinocytes that form a central plug. They can develop quite rapidly but are considered a nonaggressive form of skin cancer in that they rarely go on to spread local damage [13]. Their development is related to sun exposure.

Epidemiology Keratoacanthomas occur more commonly after age 50 and in people with fair complexions. The lesions typically develop in areas of the skin that have been previously damaged by sun or injury like the face, neck, and extremities.

Approach to the Patient

Diagnosis History A patient may report a tender nodule forming over a period of weeks to months typically starting as a small pimple then enlarges.

Physical Examination The tumors are 5 mm to 2 cm flesh-colored dome-shaped nodules with a central appearing keratin plug or necrosis.

Special Testing Biopsy is recommended to determine if the lesion is a keratoacanthoma or a more aggressive type of squamous cell carcinoma.

Differential Diagnosis Aggressive SCC, sebaceous cyst, molluscum, epidermal inclusion cyst, dermatofibroma.

Treatment Removal of the entire lesion is warranted and is typically done best by excisional biopsy. If a lesion is large, a partial shave may be acceptable with complete excision necessary if pathology shows a squamous cell carcinoma. An incomplete excision will require follow-up curettage and electrodesiccation.

Referrals Dermatology or general surgeon consultation is advisable with a very large lesion or one in a technically difficult area.

Counseling Patients should be warned of potential scarring or incomplete removal prior to performing excision.

Patient Education and Activation Patients should be advised to use sun protection with sunscreen and clothing.

Vulvar SCC

General Principles

Definition Vulvar SCC is a variant of SCC that typically arises from the HPV virus [14]. It is often discovered late in its course and has the potential to metastasize.

Epidemiology Vulvar SCC occurs in females over 35, more commonly in patients exposed to HPV, immunocompromised, or with preexisting skin conditions of the vulva area.

Classification

Keratinizing Non-HPV-associated SCC that is more likely to have ridges or crusts on physical examination.

Bowenoid HPV-associated flat thickened SCC.

Vulvar Intraepithelial Neoplasia (VIN) In situ vulvar SCC.

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Approach to the Patient

Diagnosis History Many patients may report no symptoms or itching, pain, and bleeding. They may notice ulcers, vaginal discharge, or dysuria. Patients may be reluctant to discuss symptoms or bring lesions to the attention of the physician.

Physical Examination Appearance of vulvar SCC and vulvar intraepithelial neoplasia (VIN) can be quite variable. Lesions may take on a whitish, red, or hyperpigmented appearance with patches of thickened skin. Other lesions may have a crusty, verrucous, or even ulcerated appearance. Often there are multiple lesions.

Laboratory and Imaging Special staining of p53 and MIB-1 protein can be done on biopsy specimens to predict aggressiveness [14].

Special Testing Colposcopy with the use of diluted acetic acid or toluidine blue to enhance lesions can be done on the vulva and nearby areas. Multiple biopsies are recommended and should be done via punch or excision. The physician who is comfortable performing a punch biopsy on other parts of the body should be able to do one with the same methods used on regular skin.

Differential Diagnosis Lichen sclerosis, lentigo, mucous cyst, acrochordon, tinea cruris, condyloma.

Treatment Therapy is based on the extent of dysplasia. Vulvar epithelial neoplasia II and III and SCC in situ are often treated with surgery. Adjuvant treatment is often needed for and is beyond the scope of this chapter. Radiotherapy, chemotherapy, and topical therapies are also used.

Medications 5FU cream is used for VIN lesions, but its use is limited by side effects.

Referrals Consultation with a dermatologist or gynecologic oncologist is necessary for complex or complicated lesions.

Counseling Patients undergoing biopsy should be counseled on potential need for multiple biopsies.

Patient Education and Activation Patients should be instructed to return to the physician if they have any recurrent symptoms.

Kaposi's Sarcoma (KS)

General Principles

Definition Kaposi's sarcomas are opportunistic malignant vascular neoplasms consisting of endothelial cells proliferating within the tumor. They are associated with human herpes virus 8 – HHV8 [2, 15] – which has a receptor that promotes endothelial cell proliferation. HHV8 has been found in all lesions. Lesions can be found on the skin, oral cavity, gastrointestinal tract, lymph nodes, or respiratory tract.

Epidemiology The incidence and type of KS varies by country; in the USA it is more common in males and HIV-positive patients.

Classification

Classic KS These are most often found on the legs of men of Italian or Eastern European descent.

African KS This is an endemic type of KS involving the lymph nodes most common in equatorial Africa most often in young men and children.

Immunosuppressed KS These occur in patients with HIV or organ transplant patients.

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Approach to the Patient

Diagnosis History Patients will typically report the appearance of a purple painful lesion that appeared over time.

Physical Examination The classic lesion is a red or purple nodule 3–15 mm in size. However, KS lesions can also be in the form of patches or macules and are often multiple. Oral lesions may be flat or nodular. The entire skin should be examined for other lesions as well as palpation of the nearby lymph nodes.

Laboratory and Imaging Biopsy is necessary for diagnosis. Chest x-rays are sometimes performed after the diagnosis is made as well as GI evaluation or bronchoscopy if disease is suspected elsewhere. HIV testing should be considered in patients presenting with KS.

Special Testing Biopsy is necessary to make the diagnosis.

Differential Diagnosis Pyogenic granuloma, nodular melanoma, hemangioma, hematoma, purpura, bacillary angiomatosis.

Treatment Therapy varies depending on the type of Kaposi's sarcoma. Initial treatment includes excision by excisional biopsy. Curative treatment includes electrodessication and curettage, cryosurgery, or radiation therapy [15].

Medications Complex cases may require intralesional or systemic chemotherapy. Patients should be treated for reversible immunosuppression such as the case of HIV disease. Removing immunosuppressants may improve disease if medically feasible.

Referrals Consultation with a dermatologist or oncologist is necessary for treatment.

Counseling Patients should be warned of potential scarring with biopsy.

Patient Education Patients should be educated on the signs and symptoms of recurrent disease.

Vascular Lesions

Hemangioma (HM) aka Strawberry Hemangioma

General Principles

Definition Hemangiomas are benign vascular growths made up of blood vessels. They can grow quite rapidly in the first month of life, and they can continue to grow up until six months and then recede by the elementary school age [2, 4].

Epidemiology They occur in infants within the first month of life; there is a slight female predilection.

Classification

Infantile aka Strawberry Hemangiomas These are superficial, typically first noticed as an area of red pigmentation on an infant's skin some time after birth. They proceed to grow up from the surface up until about two years of age and then recede. Thirty percent are present at birth, while the remaining appear within the first few weeks of life.

Cavernous Hemangiomas aka Deep Hemangiomas These occur in infancy and are typically of a deeper color. They are larger than strawberry hemangioma, often multiple, and may involve deeper tissue levels. Cavernous HM tend to persist over time.

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Approach to the Patient

Diagnosis **History** Parents will typically report seeing a red area on the skin that appears to be growing over time. Parents may report bleeding in lesions that are prone to friction.

Physical Examination In the early phase of hemangioma development, the physician may only see a flat red spot. After several weeks, the HM will feel more like a red spongy mass. Deeper lesions can take on purple coloring.

Laboratory and Imaging MRI may be considered in large, deep, or spinal hemangioma to delineate the extent of the lesion.

Special Testing Hemangiomas that lay on the midline of the spine may be related to neural tube defects and referral to a specialist is recommended.

Differential Diagnosis Pyogenic granuloma.

Treatment Most hemangiomas can be left alone to spontaneously recede. Irritated lesions or ones that obstruct vision or impede function should be considered for treatment. Pulsed dye laser treatment and surgery have been used for larger lesions or those affecting function; however, newer medical treatments have enjoyed success.

Behavioral Parents should be reassured that most HMs cause no symptoms to the patient; on occasion larger ones prone to friction should be protected.

Medications Oral propranolol is a newer very successful treatment in shrinking HMs [16] and should be prescribed by a provider with experience in dosing. Prednisone given orally can also be used to shrink HMs but often causes side effects.

Referrals Pediatric dermatology or pediatric surgeon consultation should be done when a lesion is large, ulcerating, or compromising function.

Counseling Physicians should review side effects of oral treatments and surgical treatments with patients prior to treatment.

Patient Education and Activation Parents should be reassured that most hemangiomas will recede over time resulting in a much smaller lesion.

Cherry Angioma

General Principles

Definition Angiomas are very small acquired vascular neoplasms made up of proliferating capillaries [2]. They are found in most adults.

Epidemiology They typically occur in patients over the age of 30 and increase in number as patients age.

Approach to the Patient

Diagnosis **History** Most patients will report a painless red bump or bumps on their skin.

Physical Examination Angiomas are 0.5–5 mm round vascular papules. Color can range from cherry red to deep purple, and they are most often found on the torso.

Special Testing Shave biopsy may be needed for larger lesions if there is a concern for malignancy.

Differential Diagnosis Telangiectasia, pyogenic granuloma, petechiae, bacillary angiomatosis, melanoma.

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Treatment Therapy is typically unnecessary; however, if patients desire for cosmetic reasons, there are several options.

Pulsed dye laser therapy, cryotherapy, and electrocautery are all quite effective [17].

Counseling Patients should be warned of the risks of scarring or depigmentation prior to treatment.

Patient Education and Activation Patients should be reassured that these are benign entities and adults tend to acquire more as they age.

Angiokeratoma

General Principles

Definition Angiokeratoma are vascular papules arising from dilated blood vessels with epidermal hyperkeratosis. They more commonly appear as multiple lesions clustered in one area, often on the scrotum or vulvar areas. Increased venous pressure has been implicated in their formation [4].

Epidemiology They may appear during childhood or adulthood depending on the type.

Classification

Angiokeratoma of Fordyce Multiple angiomas on the scrotum or vulva.

Solitary Angiokeratoma Single lesions.

Angiokeratoma of Mibelli An autosomal dominant disorder with painful lesions on the dorsal surfaces of the digits.

Fabry's Disease An X-linked inborn error that leads to formation of angiokeratomas in a bathing-suit distribution around puberty.

Approach to the Patient

Diagnosis History A patient will report a typically painless dark spot/spots.

Physical Examination Angiokeratomas are 0.5–5 mm papules that can be red, purple, or black. Dermoscopy examination reveals obvious vascular lacunae within a papule.

Special Testing Biopsy is not typically required but if performed will show blood vessel dilatation with hyperkeratosis.

Differential Diagnosis Hemangioma, melanoma, Kaposi's sarcoma, pyogenic granuloma.

Treatment Therapy is typically only necessary for cosmetic reasons. Electrocautery and laser therapy are effective.

Referrals Consultation with a dermatologist may be necessary for laser treatment. Treatment associated with Fabry's disease is directed at the underlying disease.

Counseling Patients should be warned of potential scarring from treatment.

Patient Education and Activation Patients should be reassured that genital angiokeratomas are not sexually transmissible.

Venous Lake

General Principles

Definition Venous lakes are made up of a dilated portion of a vein on previously damaged skin.

Epidemiology They are more common in older patients on sun-damaged skin. The face, lips, and ears are common sites.

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Approach to the Patient

Diagnosis History Most patients will not be seeing a very dark spot on their skin or lips. Raised lesions may cause symptoms of itching or soreness especially if they become thrombosed.

Physical Examination Venous lakes are typically 3–10 mm in size. Coloring can be purple, red, or black. Dermoscopy examination will show the telltale grapelike congregation of vascular lacunae [3].

Special Testing Biopsy is not necessary.

Differential Diagnosis Malignant melanoma, venous varicosity, melanoma, Kaposi's sarcoma.

Treatment Therapy is generally not indicated unless the lesion is repeatedly traumatized. Laser can be effective as well as surgically unroofing the lesion and cauterizing the base.

Referrals Dermatology consultation may be needed for laser treatment or changing lesions.

Counseling Patients should be warned of potential scarring from treatment.

Patient Education and Activation Patients should be warned to avoid the sun and protect their skin with sunscreen and clothing.

Pyogenic Granuloma (PG)

General Principles

Definition These benign lesions are vascular growths that arise in the skin or oral mucosa in reaction to small trauma. Histologically, they contain proliferating endothelial cells and fibroblasts [2].

Epidemiology Most often PGs occur in young adults and children, and they affect both genders equally.

Approach to the Patient

Diagnosis History Patients will commonly give the story of a new onset yellow or red lump that bleeds easily with just minor pressure. Occasionally patients will be able to give a history of preceding trauma and a lesion forming during the healing process. Patients may report mild soreness. If the patient's medical history includes immunosuppression or HIV, Kaposi's sarcoma should be considered.

Physical Examination Pyogenic granulomas tend to appear as moist red/rust-colored papules 4–15 mm in size. Some will have yellow discharge overlying the papule (Fig. 5). There may be a surrounding collarette of the skin at the narrowed base. PGs are friable with contact bleeding with only minor trauma.

Special Testing A lesion should be sent for pathology if there's any question that it may be something other than a pyogenic granuloma.

Differential Diagnosis Nodular melanoma, Kaposi's sarcoma, bacillary angiomatosis, angiosarcoma.

Treatment PGs should be removed surgically with a shave-type procedure followed by electrodesiccation or curettage of the base of the granuloma. PGs may bleed quite a bit during removal; however, when the lesion is completely removed, the bleeding typically slows down. Silver nitrate or aluminum chloride applied to the base will stop further bleeding. Occasionally adequate treatment or failure to remove all of the granuloma will lead to its recurrence, which can be treated with repeat curettage.

Referrals Consultation with dermatology is helpful for multiple or recurring PGs or if the diagnosis is in doubt.

Counseling Patients should be warned of the possibility of a small scar after removal.

Patient Education and Activation Patients can be reassured this is a benign lesion; however, if it does not heal completely and act as expected after removal, they should be urged to follow up.

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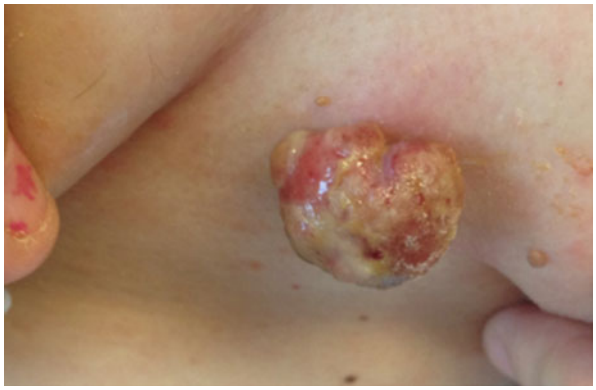

Fig. 5 This large pyogenic granuloma formed within 2 days

Nonpigmented Nonvascular Lesions

Dermatofibroma aka Fibrous Histiocytoma

General Principles

Definition Dermatofibromas are skin lesions made up of dendritic histiocyte cells. They may arise in reaction to a minor injury such as an insect bite or develop spontaneously [18].

Epidemiology They are more common in women especially on the lower legs or arms.

Approach to the Patient

Diagnosis History Most patients will not recall any trauma and some will have symptoms of mild itching. Typically the lesion will have been present for several months to years, grown to a certain size and remained stable.

Physical Examination Inspection will reveal a 3–8 mm firm, rubbery papule fixed within the skin. They are usually pink, tan, or brown in color often with a central pale area and darker red or brown toward the periphery. The skin will dimple over the lesion when the dermatofibroma is pinched on both sides. Dermoscopy will reveal a large central pale to white patch [3].

Special Testing Biopsy is not required to make the diagnosis; however, on some occasions, it may be necessary to reassure the patient and/or provider.

Differential Diagnosis Amelanotic melanoma, dermatofibrosarcoma, keloid.

Treatment It is not required; however, some patients may want removal for cosmetic reasons. Cryotherapy can be attempted to decrease the size, but it may result in hypopigmentation of the area. Punch or excisional biopsy can be performed for removal but may result in scar.

Medications Creams are not effective in decreasing the appearance or size of a dermatofibroma.

Referrals Consultation with a dermatologist can be done if there is doubt to the diagnosis.

Counseling Patients who request removal should be counseled that the scar may be of similar size to the original dermatofibroma.

Patient Education and Activation Patients should be told that the lesion will likely persist indefinitely, but if unexpected change in size occurs, they should return to their physician.

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Keloid/Hypertrophic Scar

General Principles

Definition A keloid is a fibroproliferative response to a skin injury. The subsequent keloid will be larger than the original injury. True keloids will not regress with time unlike hypertrophic scars which are of different etiology and may regress [4, 19]. Hypertrophic scars are an exaggerated response to healing that does not extend beyond the scars' original size.

Epidemiology Keloids occur with equal frequency in men and women. They are more common before age 30, in darkly pigmented skin and over the chest and back where the skin is under more tension while healing. Hypertrophic scars do not show a racial difference.

Approach to the Patient

Diagnosis **History** Patients will typically recall an event of skin disruption such as a piercing, surgery, or burn within one year of keloid formation. There may be itching or mild pain.

Physical Examination Coloring can range from flesh colored to red. They can range from soft to very firm to the touch.

Special Testing Biopsy is not necessary for diagnosis.

Differential Diagnosis Hypertrophic scar, dermatofibroma, sarcoidosis, dermatofibrosarcoma.

Treatment Surgical removal or correction should only be attempted by experienced surgeons as adjunctive treatments to limit reformation will likely be necessary. Laser has shown promise for very vascular scars.

Behavioral Silicone gel sheets applied during healing may prevent formation of keloids in susceptible patients but research is not entirely convincing.

Medications Injecting a keloid with intralesional triamcinolone 10–40 mg/ml can decrease the size and symptoms but may need to be repeated every 2–4 weeks. Imiquimod may be marginally effective.

Referrals Dermatology, plastic surgery, or general surgery consultation may be necessary for treatment of large keloids.

Counseling Patients should understand that any surgical treatment may result in subsequent scarring.

Patient Education and Activation Due to the nature and difficulty of treating keloids, the physician should be understanding of the distress a patient may feel in becoming scarred. Patients at risk of keloids should also consider not having elective cosmetic procedures due to the risk of keloid formation.

Lipoma

General Principles

Definition A lipoma is a benign growth composed of grouping of adipocytes in a fibrous capsule [2, 20].

Epidemiology They most often occur in adulthood on areas of the body that contain more fat.

Classification

Hereditary Multiple Lipomatosis An autosomal dominant condition of multiple lipomas in males.

Pleomorphic Lipomas that contain adipocytes and giant cells.

Angiolipoma A lipoma variant with adipocytes and vascular proliferation.

Spindle Cell Lipoma A variant containing spindle cells.

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Approach to the Patient

Diagnosis History Most patients will report a slowly growing lump under their skin that is nonpainful.

Physical Examination A mild swelling may be seen under the skin. Palpation typically reveals a soft to medium firm lump that is not fixed to the overlying skin.

Special Testing MRIs can be used to determine if fast-growing lesions are more consistent with liposarcomas.

Differential Diagnosis Epidermal cyst, liposarcoma.

Treatment No treatment is necessary for most lipomas; however, patients may desire removal secondary to discomfort from large lipomas or for cosmetic reasons. Surgical excision is the most common treatment and several different techniques exist [20]. Enucleation can be performed by cutting a 5 mm incision, freeing the underlying lipoma from the surrounding tissue and extruding it through the incision. Excision can be also performed via traditional surgical excision or by cutting an ellipse of the skin overlying the lipoma then dissecting the lipoma from the surrounding tissues and suturing the defect closed. Liposuction can be used to decrease the size of a lipoma.

Medications Injection with triamcinolone 10 mg/ml with lidocaine may be repeated monthly several times to shrink a lipoma.

Referrals Consultation with a dermatologist or general surgeon may be necessary in the case of large lipomas or those overlying sensitive structures.

Counseling Patients should be warned of potential for scarring or damage to underlying tissues during removal.

Patient Education and Activation Patients can be reassured that these are benign, and if they grow quickly or become symptomatic, they should follow up with their physician.

Epidermal Inclusion Cyst (EC)/Sebaceous Cyst

General Principles

Definition Epidermal cysts are collections of keratin within a cyst felt under the skin. They arise from hair follicles within the epidermis.

Classification

Milia One to two millimeter epidermal cysts typically on the face are typically very firm and will stay solid when extruded.

Wen/Pilar Cyst Cysts in hair-bearing areas, they have thick walls that line the cyst.

Ruptured Sebaceous Cyst Due to the thin-walled nature of ECs, they commonly rupture under the skin and produce a severe inflammatory reaction.

Gardner's Syndrome Multiple sebaceous cysts may be related to Gardner's syndrome, which is an autosomal dominant condition associated with colon polyps and potentially colon cancer.

Epidemiology ECs typically occur after puberty or in adulthood most commonly on the face, neck, posterior ears, or trunk.

Approach to the Patient

Diagnosis History Patients typically will complain of a small bump in their skin sometimes knowing of its presence for several months or they may have just discovered it. Occasionally with an inflamed cyst a

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patient will report that they had a small bump that suddenly grew overnight to a hard red painful area resembling an abscess.

Physical Examination It typically reveals a hard nonpainful lump 0.5–5 cm in size. There may be a pore over the cyst with plugged keratin underneath. Ruptured cysts are typically red, warm, and very tender. At times they will be oozing inflammatory products.

Laboratory and Imaging Culture of ruptured cysts is not recommended as they are not infected.

Special Testing On occasion an abnormal-appearing cyst may be sent to pathology if the diagnosis is uncertain.

Differential Diagnosis Lipoma, keratoacanthoma, abscess.

Treatment Small asymptomatic cysts do not need to be removed. However, cysts typically will enlarge over time, so in areas where they are likely to be traumatized, are symptomatic, or affect cosmesis, removal is recommended.

Ruptured cysts should be incised and the contents drained. However, complete removal of the cyst may be difficult due to adherence or scarring of the cyst wall, and removal may be best done after inflammation resolves.

Excision [21] of the cyst can be done through a minimally invasive technique of making a 3–4 mm incision (or punch biopsy), removing the cyst contents, and then pulling the cyst out through the incision and removing it. Alternatively a larger incision can be made, the cyst freed from the surrounding tissues and removed in total.

Behavioral Medications Antibiotics are not indicated in the case of a ruptured cyst as these are not infected.

Referrals Consultation with plastic surgery or dermatology may be necessary in cysts over cosmetically vulnerable areas.

Counseling Patients should be warned of possible scarring or incomplete removal of cyst prior to removal.

Patient Education and Activation Patients should be advised that cysts may increase in size or rupture.

Oral Lesions

Leukoplakia

General Principles

Definition It is a term used to describe a white lesion of the oral mucosa that cannot be wiped off [22]. Most lesions are due to hyperkeratosis or irritants and will resolve in a short time; however, 25 % of lesions contain dysplastic cells and may progress to SCC/oral cancer. Lesions on the floor of the mouth or ventral tongue or nodular in appearance are more likely to be premalignant.

Epidemiology Leukoplakia typically occurs after age 40. It is more common in males, tobacco users, and those exposed to HPV.

Classification

Erythroplakia A focal red area within a leukoplakia patch [23].

Oral Hairy Leukoplakia EBV-associated variant often on the lateral tongues of patients with HPV [2].

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Approach to the Patient

Diagnosis History Patients may have seen the lesion and occasionally will have soreness or noticed mild bleeding, but they typically have no symptoms.

Physical Examination It will show a white patch or plaque in oral mucosa most commonly seen in the buccal mucosa, floor of the mouth, or lower lip. Red areas (erythroplakia) may also be seen. Lymph node examination should be performed. Lesions may appear verrucous, and these lesions are higher risk for malignancy.

Laboratory and Imaging There is currently no recommendation for HPV swabbing for lesions although research is in progress.

Special Testing Biopsy should be performed in tobacco users if a lesion is thick, is changing, or has any erythroplakia. Biopsy should also be performed if the lesion does not resolve after 14 days of observation or after removing potential irritants. Toluidine blue is a substance that can be applied to a leukoplakia; it binds preferentially to areas of high DNA concentration and may guide the practitioner to biopsy a more concerning area.

Differential Diagnosis Thrush, lichen planus, oral hairy leukoplakia, squamous cell carcinoma, frictional keratosis.

Treatment Therapy depends on the degree of dysplasia on a biopsy sample [22]. Mild dysplasia can be observed with follow-up to assess for clinical change. Removal is indicated in moderate-to-severe dysplasia, and excision with scalpel or CO2 laser can be performed. Cryosurgery and electrosurgery are also used for treatment. Patients should be encouraged to follow up to assess for clinical recurrence.

Behavioral Patients should be encouraged to refrain from irritating substances and tobacco products.

Medications 5FU is used in treatment.

Referrals Consultation with an experienced oral surgeon or otolaryngologist may be necessary for biopsy or treatment.

Counseling Patients should be warned of the malignant potential of lesion and those that will become cancerous can do it within 6 months to several years.

Patient Education and Activation Patients should be encouraged to quit tobacco products if used and if a lesion persists patients should have a follow-up with their physician.

Erythroplakia

General Principles

Definition Erythroplakia is an oral lesion with red qualities that cannot be wiped off. Malignancy potential is high, as 90 % will contain premalignant cells [22].

Epidemiology It is similar to leukoplakia with a higher incidence in smokers and males.

Approach to the Patient

Diagnosis History Patients often have no symptoms, but pain and bleeding can occur.

Physical Examination Erythroplakia have a flat or velvety appearance, and color can range from pink to red, typically heterogenous with areas of hyperkeratosis. Lymph nodes should also be examined.

Special Testing. Biopsy should be performed expediently by the physician or specialist. If a partial biopsy is to be done, getting a sample of the thickest part of the lesion is more likely to show pathology.

Differential Diagnosis Mucocele, lichen planus, SCC.

Treatment Excision should be performed surgically or with CO2 laser.

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Behavioral Patients should refrain from irritating substances or tobacco products.

Referrals Consultation with an otolaryngologist or oral surgeon may be necessary for biopsy or removal of some lesions.

Patient Education and Activation Patients should be counseled to avoid tobacco products and alcohol as well as monitoring for reoccurrence.

Surgical Techniques

Physicians will find themselves removing lesions that are malignant, potentially malignant, and benign. The decision to remove benign lesions should be done only after careful consideration and discussion with the patient of possible complications. Areas of potential for poor healing such as the lower leg should be done with caution. Scarring can occasionally be worse than the original lesion especially on areas that heal poorly or are prone to form keloids (chest/back).

Presumed malignant lesions should be removed in total whenever possible depending on the size of lesion and location [17]. Elliptical excision is the desired method of removing cancerous lesions including a 2 to 3 mm margin of normal skin. Punch biopsy may be an accepted course when lesion can be completely removed with a punch or in the case of a very large lesion where waiting for an excision may delay diagnosis or a patient may be unable to travel to get a more difficult biopsy done.

A **shave excision** is typically done on bumpy lesions such as pyogenic granuloma, dermal nevi, and skin tags. It may be acceptable on lesions such as squamous cell carcinoma or basal cell carcinoma in areas where removal of excessive skin would be difficult and the patient understands that another treatment may be necessary if pathology reveals an incomplete excision. One should be very hesitant to perform a shave biopsy on a suspected melanoma, as bisecting the depth of a melanoma would highly affect the ability to stage the melanoma accurately. The shave biopsy procedure [17] includes marking the lesion and landmarks prior (as epinephrine may cause blanching and disappearance of vascular landmarks) to numbing the lesion with lidocaine with or without epinephrine, prepping the skin with ChloraPrep or Betadine, and removing the lesion to the level of the mid-dermis. A shave may be performed with a scalpel, razor blade, or DermaBlade. Hemostasis can be achieved by application of aluminum chloride, pressure, or silver nitrate.

Shave biopsies offer the benefit of removing less skin and in most cases providing the patient with a diagnosis without cutting through to the dermis which enables improved healing and less bleeding.

Excisional biopsy is most commonly done to remove a suspected melanoma, BCC, SCC, or dermatofibroma. The lesion and ellipse should be marked prior to anesthesia as epinephrine may cause a lesion to blanch and borders may become indistinct prior to excision. The area should be anesthetized with lidocaine with or without epinephrine. The area should then be cleansed with alcohol, ChloraPrep, or povidone-iodine. The lesion should be removed with a 2 to 4 mm margin. Care must be taken to the scalpel perpendicular to the lesion so as not to partially bisect the lesion while removing it. Also orienting the ellipse longitudinally on extremities or in the area of the skin lines can be helpful with healing. The biopsy site should be close with interrupted sutures and left in for 7–21 days depending on the site.

Punch biopsy is most often used to assist in diagnosis or remove small lesions. The area is first anesthetized with lidocaine with or without epinephrine. The skin should be cleansed with alcohol and a sterile punch tool is used to enter the skin and rotated clockwise and counter clockwise through the dermis to the subdermal fat. The specimen is then cut free from the underlying fat and sent to the lab. A 2–3 mm punch can often be closed with just an adhesive tape such as Steri-Strips, while a 4–6 mm punch may require a suture.

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Table 3 Biopsy methods for skin cancers

Shave	Excisional	Electrodessication	Cryotherapy
SCC	Malignant melanoma	SCC	Thin SCC
BCC	SCC	BCC	Actinic keratosis
Nevus	BCC	Pyogenic granuloma	Dermatofibroma
	Lipoma	Cherry angioma	Seborrheic keratosis
	Sebaceous cyst	Sebaceous hyperplasia	Leukoplakia
	Pyogenic granuloma	Actinic keratosis	

Curettage and **electrodesiccation** [17] can be used to destroy small benign lesions or as a complementary procedure to treat an incompletely removed small or superficial SCC or BCC. The area is anesthetized with lidocaine and then a curette is used to scrape away the remaining lesion. This is done by sight and touch as malignant lesions are often softer. The area is then curetted until firm normal/gritty skin can be felt underneath. The site is then desiccated/burned to the base with electrocautery. This is repeated two more times. The electrocautery has the advantage of achieving hemostasis.

Cryotherapy can be used for treatment of superficial lesions but can cause hypopigmentation or potentially incomplete treatment. Shorter freezing times of 5–15 s can be used for thin lesions like actinic keratosis. Longer freezing times for two cycles of 30 s each are required for thin BCC or SCC (Table 3).

Principles of Sun Exposure Protection/Sunscreen

UVA light is generally stronger and more damaging and penetrates deeply to the mid-dermis. There is no seasonal variation, it is found in tanning beds, and it causes aging of the skin, photo eruptions, and skin cancer.

UVB light is stronger in the summer and at midday; penetration increases with higher altitudes, and UVB causes sunburn, skin cancer, and cataracts.

Exposure to sun during midday and at altitude increases sun damage.

Sunscreen

Sunscreens work by either absorbing or reflecting the sun's rays.

Absorbing "organic" sunscreens contain the active ingredients benzophenones, anthranilates, oxybenzone, or PABA.

Reflecting sunscreens contain zinc oxide and titanium dioxide.

Broad-spectrum sunscreens provide UVA and UVB protection in turn reducing sunburn, skin cancer, AKs, SCC, and melanoma.

SPF protection denotes that higher numbers limit greater amounts of UVB exposure; SPF $>$ 30 or 50 is considered protective.

Most patients use less sunscreen than needed and do not reapply often enough. Adult face requires one tsp for coverage and the body two to three tablespoons. Sunscreens should be applied 30 min prior to sun exposure and reapplied every 2 h. Most water-resistant sunscreens will be useless after 30 min of water activity.

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Family Medicine
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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 may be autoimmune in nature, but the pathogenesis is not understood. Approximately 1 % of the population is affected with no propensity in either gender. 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 [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, 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. 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. 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 the hands or feet, responds poorly to treatment. Treatment usually takes 6–12 months and should be started early in the course of disease. Narrowband ultraviolet B (UVB) is more effective than psoralen plus ultraviolet A radiation (PUVA) and is recommended as the first-line treatment for generalized vitiligo [2]. Moderate-potency topical steroids, or topical calcineurin inhibitors (tacrolimus and pimecrolimus), for 6–9 months are preferred for localized vitiligo [2]. 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.

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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 [4]. The lesions begin as a nonspecific erythema but gradually become scaly and hypopigmented. 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. Treatment consists of topical emollients, which have shown to be just as effective as any medicated topical treatment [3]. High-potency topical steroids can be used on erythematous inflammatory lesions, but the depigmentation is not affected by any treatment. Pimecrolimus cream 1 % and tacrolimus ointment (0.03 % or 0.1 %) are nonsteroidal alternatives for treatment.

Tuberous Sclerosis

Tuberous sclerosis (TS) is the second most common neurocutaneous syndrome, affecting 1 in 6,000 newborns, and is marked by childhood seizures and mental retardation but can affect several organ systems [5]. 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 [6]. Skin manifestations may be the earliest sign of TS and occur in 80 % of patients by 1 year of age [7]. 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 not truly a hyperpigmentation disorder, but involved skin may appear darker than normal, and it is a common presenting complaint for family physicians. Increased sebum production during puberty allows the proliferation of *Pityrosporum ovale* or *Malassezia furfur*, which causes brown, pink, or reddish skin discoloration that may be scaly and pruritic [8]. Potassium hydroxide preparation is positive for fungal elements, and Wood's lamp examination can reveal yellow to yellow-green fluorescence. Both topical and oral antifungal treatments are effective. Topical therapy is preferred for localized disease and systemic therapy for recurrent or widespread lesions. Topical selenium sulfide 2.5 % applied for 10 min daily for 7 days and 2 % ketoconazole shampoo applied to affected areas for 5 min prior to showering for three consecutive days are effective regimens [9]. Topical antifungal agents are also effective but require daily use for approximately 14 days. 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 [10]. Oral terbinafine 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 [11]. Reactions can range from imperceptible erythema followed by prolonged hyperpigmentation to a

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sunburn-like reaction, edema with vesicles, and bullae [12]. Common medications associated with photosensitivity include antibiotics (fluoroquinolones, sulfonamides, tetracyclines), diuretics (furosemide, hydrochlorothiazide), diltiazem, nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, and topical retinoids. Common foods include lemons, limes, celery, dill, and carrot juice [11]. 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 [13]. 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.

Clinical Presentation

Clinical features are characteristic and follow the five P's of lichen planus: pruritic, planar, polyangular, purple, and 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 the flexor surfaces of the wrists, forearms, and legs [14]. 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 [14]. 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 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 [13]. Azathioprine can be used as an alternative 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 and pimecrolimus, and aloe vera gel have all been shown to be effective in treating mucous membrane LP if topical steroids are not tolerated [13]. 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 [15]. 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.

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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 [16]. 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 [16]. 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. Both non-scarring and scarring alopecia occur in more than 20 % of cases of SLE [16].

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 [16]. 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. If topical steroids fail, antimalarial medications such as hydroxychloroquine or chloroquine are indicated [16]. 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 and 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 [17]. Risk factors include poorly fitting shoes and anatomical pathology (bunions, hammer toes, claw toes, elevated metatarsals, and varus or valgus inverted hindfoot) 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 [17]. 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

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heads. In contrast to corns, calluses do not possess a conical core and have undefined margins [17]. 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 or changing footwear can be helpful in patients with foot abnormalities, such as pes planus. Symptomatic relief of a hard corn can often be achieved through debridement of the lesions and removal of the keratin plug [17]. 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 [18]. 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 [19]. 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 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 [20]. 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. The diagnosis of onychomycosis should be confirmed because the treatment is long and potentially expensive; however, the involvement of multiple toes or concomitant tinea pedis may justify treatment without confirmation [20]. Fingernail infections are generally caused by the *Candida albicans* species and are associated with chronic mucocutaneous candidiasis.

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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 % [21]. 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 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 [19]. 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. Liver function testing should occur prior to, and one month after, initiating therapy. 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 [21]. 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 [22]. 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 [23]. 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. The most common 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 [23]. 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 [24]. 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

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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.

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) [25]. 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 [26]. 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 [26]. Physical examination typically reveals generalized hair loss as well as a positive hair pull test [25]. Taking 40–60 hairs between your thumb and forefinger and sliding down the length of the hair while holding a steady traction on the hairs complete the test. The test is considered positive if greater than 10 % of the hairs are removed. Treatment consists of stress reduction or identifying a medical cause [26]. 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 typically cause this, though inflammatory diseases such as alopecia areata and pemphigus are also culprits [27]. 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 [28]. Hair follicle stem cells are spared from destruction; therefore, the hair loss from anagen effluvium is not permanent [29]. 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 [25]. The onset of the

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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 % [30]. 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 [31]. 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 [32]. Topical minoxidil 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 [26].

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 alopecias, the follicles are destroyed by a non-follicular process such as neoplasm, radiation, infection, surgery, and physical or chemical burns [31]. 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 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 include tight braiding (traction alopecia), 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. Treatment is removal of the practice that caused the hair trauma.

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.

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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 [20]. 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 and Diflucan have equal effectiveness and safety and shorter treatment courses [20]. 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 [20]. 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 and oral finasteride. 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 [33]. 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 [33]. 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. Possible surgical approaches for androgenic alopecia include follicle transplant, scalp reduction, and a transition flap.

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Dyslipidemias

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1 General Principles

1.1 Definition of Dyslipidemias

Dyslipidemias are disorders encompassing 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 are not synonymous to desirable (optimal or physiological) levels. Dyslipidemias are of extreme clinical importance due to their association with atherosclerosis and rates of heart attack and stroke. The desirable 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 above normal when >150 mg/dL after a 12 h fast [1].

1.2 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 (e.g., NMR LipoProfile™) or by surrogate markers (e.g., ApoB or ApoA1 levels). Chylomicrons are synthesized in the intestinal epithelium (TG:C ratio 10:1). The liver synthesizes very low-density lipoprotein VLDL-P (TG:C ratio 5:1), hydrolyzed in circulation to intermediate (IDL-P), and then low-density lipoprotein (LDL-P), which hardly contain any TG. LDL-P and other ApoB-containing lipoproteins (e.g., chylomicron remnants, 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 the plaque to the liver and therefore is thought to be beneficial. Circulating LDL-P is bound to LDL receptors on hepatocytes. This complex is endocytosed. LDL-P is degraded, while the LDL receptor is recycled to the cell surface to bind more LDL-Ps. However, PCSK9 (proprotein convertase subtilisin/kexin type 9), a protein secreted by hepatocytes, binds to LDL receptors preventing their recycling and leading to their degradation. Cholesteryl ester transfer protein (CETP) mediates the exchange of 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, cholesterol-poor HDL-Ps, which are unstable and release ApoA1, which is lost in the urine leading to decreased HDL-C [2, 3].

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1.3 Epidemiology

Western lifestyle increases the prevalence of dyslipidemia worldwide. In the USA, an estimated 53 % of adults have less than perfect lipid levels: 27 % have high LDL-C, 23 % have low HDL-C, and 30 % have high TG. 21 % of US adults have mixed dyslipidemia (high LDL-C with either low HDL-C and/or high TG). Nearly 6 % have all three abnormalities [4].

1.4 Screening for Dyslipidemias in Adults

Screening for dyslipidemias is recommended by the US Preventive Services Task Force (USPSTF) with Grade A recommendation in (1) men aged ≥35 years; (2) men aged 20–35 years, if at increased risk for coronary heart disease (CHD); and (3) women aged ≥45 years, if at increased risk for CHD. Screening women aged 20–45 years at increased risk for CHD has a Grade B recommendation. No recommendation is made for or against screening in men aged 20–35 years or women aged ≥20 years, not at increased risk for CHD (Grade C). Increased risk for CHD includes diabetes mellitus (DM), previous personal history of CHD or noncoronary atherosclerosis, tobacco use, hypertension, obesity, and family history of CHD in males aged <50 and females aged <60. The preferred screening method is total cholesterol (TC) and HDL-C on fasting or non-fasting samples. The optimal interval for screening is uncertain. Every 5 years is reasonable, with shorter intervals for people with dyslipidemia. An age to stop screening has not been established [5]. The National Lipid Association (NLA) recommends screening all adults (≥20 years) with a fasting or non-fasting lipid profile (LP) every 5 years [1].

1.5 Screening for Dyslipidemias in Children

According to the USPSTF, evidence is insufficient to recommend for or against routine screening for dyslipidemias in infants, children, adolescents, and young adults until the age of 20 years [5]. The NIH Heart, Lung, and Blood Institute Expert Panel recommended universal screening in children aged 8–11 years and adolescents aged 17–21 years with either fasting LP or non-HDL-C [6]. The American Heart Association (AHA) recommends cholesterol screening every 4–6 years for all adults ≥20 years, but does not endorse universal screening in pediatric populations. The American Academy of Pediatrics recommends testing of children with a fasting LP or a non-fasting non-HDL-C once between age 9 and 11 [6]. Screening starting at age 2 should be considered in children with a family history of premature cardiovascular disease or elevated cholesterol [7].

1.6 Classification

Dyslipidemias can be divided into primary (genetic) and secondary. Fredrickson's classification distinguishes the following:

- *Type I (hyperchylomicronemia)*: 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.
- *Type IIa (familial hypercholesterolemia, FH)*: LDL-C usually ≥190 mg/dL, in homozygous FH (hoFH) often up to 500 mg/dL and above. Subjects with mild mutations and heterozygous FH (heFH) may have LDL-C <190 mg/dL. Early ASCVD, sometimes in children, is present. Tendon xanthomas and corneal arcus are frequent findings. FH phenotype is classically caused by LDL receptor mutations, but can be seen with mutations of ApoB or PCSK9 (gain of function). Prevalence: hoFH 1:1,000,000, heFH 1:200–1:500.
- *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.

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- *Type III (dysbetalipoproteinemia):* IDL-P 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.
- *Type V (familial 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.

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 [8].
- *Inherited low HDL-C*: hypoalphalipoproteinemia is usually associated with increased ASCVD. Rare forms include Tangier's disease and lecithin-cholesterol acyltransferase (LCAT) deficiency, which in its heterozygous form is known as fish-eye disease. It is unclear whether they are associated with higher ASCVD risk. Very rare forms of low HDL-C (such as with ApoA1 Milano) are cardioprotective.
- *Inherited high HDL-C*: very high HDL-C levels (>100 mg/dL) may not be cardioprotective, as they often reflect deficient function of HDL-P.
- *Inherited low LDL-C*: hypobetalipoproteinemia, autosomal dominant, heterozygote patients have LDL-C of 20 and less, decreased ASCVD risk. Moderate LDL-C decrease (40–60 mg/dL) and decreased ASCVD risk are seen with loss of function and PCSK9 mutations. Abetalipoproteinemia, autosomal recessive, presents in childhood (homozygotes only) with symptoms of deficiency of fat-soluble vitamins; LDL-C and VLDL-C are undetectable. Patients are at increased risk of hemorrhagic stroke.
- *Familial combined hypolipidemia*: caused by mutations of the ANGPTL3 gene; all lipid levels are very low, including HDL-C, decreased ASCVD risk.
- *Sitosterolemia*: 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, normal LDL-C levels, resulting from accumulation of cholestanol, increased ASCVD risk, mimics hoFH plus neurological abnormalities. Prevalence ∼1:50,000.
- *Cholesteryl ester storage disease aka 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

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(chronic renal disease, nephrotic syndrome), infectious (HIV, hepatitis), hepatic (obstructive liver disease, cholestasis), 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 or as increased non-HDL-C or ApoB. It correlates with increased ASCVD risk [2, 3].

2 Diagnosis of Dyslipidemias

2.1 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 children with chylomicronemia. 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.

2.2 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 that at <40 years of age is associated with dyslipidemia, later in life is a nonspecific finding. Clouding of the entire cornea from cholesterol deposits is characteristic of fish-eye disease. Eruptive xanthomas are TG accumulations in the form of small papules often with an inflammatory base, found in hyperchylomicronemia and severe hypertriglyceridemia. Fundoscopic eye exam in children suspected to have hoFH may reveal nonarteritic 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, 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, 3].

2.3 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, non-fasting 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

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with >400 mg/dL. In such case, direct LDL-C measurement is obtained. Non-fasting TC and HDL-C can be used to calculate non-HDL-C. TSH and proteinuria screen will rule out two common secondary causes of dyslipidemia. In anticipation of statin therapy, obtaining baseline LFTs, A1C, and CK levels is advised [2, 3].

Extent of preclinical atherosclerosis is measured by two noninvasive methods: carotid intima-media thickness (CIMT), obtained by US, and coronary calcium score (CCS), obtained by a limited CT scan. CCS has a higher grade of recommendation for the purpose of risk restratification in intermediate risk individuals [9].

2.4 Special Testing

Advanced lipid tests are offered by several companies (Cleveland HeartLab, Atherotech, LipoScience, Boston Heart, Berkeley HeartLab, etc.). They include combinations of measurements, obtained by different proprietary techniques, which are often discrepant. Caution is advised when using those tests, as many of them lack high-level evidence for their use, especially in the general population.

LDL-C and LDL-P can be discordant in up to 30 % of individuals, especially those with metabolic syndrome. LDL-P is a better predictor of CV risk than LDL-C [10, 11]. Increasing accuracy of surrogate markers to estimate CV risk reflects the direct association of LDL-P with atherosclerosis (LDL-P > ApoB > non-HDL-C > LDL-C > TC). LDL-P can be measured directly by tests such as NMR LipoProfile™, also providing measurement of other lipoproteins and the insulin resistance index (predicting the risk of developing type 2 DM). Canadian and NLA guidelines recommend measuring ApoB as the secondary target of therapy. Measurement of Lp(a) is reasonable in patients with family history of early ASCVD. Evaluation of two different inflammatory markers, high-sensitivity CRP and Lp-PLA2, aids in the potential restratification of patients at intermediate risk. Evidence is lacking to use HDL and LDL subfractions as well as more comprehensive inflammatory panels [2, 3, 12].

Genotyping ApoE helps diagnose dysbetalipoproteinemia (Apo E2/E2), and it can also disclose increased risk of Alzheimer's disease (Apo E4/E4). Cholestanol measurement evaluates the proportion of cholesterol from intestinal absorption vs. synthesis in order to potentially guide therapeutic decisions [2, 3].

2.5 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.

3 Treatment

Dyslipidemias, especially secondary to poor lifestyle choices, are amenable to therapeutic lifestyle modifications (TLMs). However, pharmacologic therapy is often required. According to the 2013 American College of Cardiology (ACC)/AHA recommendations, statin therapy is based on a global assessment of risk and potential benefit of treatment evidenced in randomized controlled trials (RCTs) without the need of using targets of therapy (Fig. 1). The 2013 ACC/AHA guidelines emphasize statin treatment in four statin benefit groups: (1) patients with established ASCVD, (2) patients with LDL-C ≥190 mg/dL, (3) patients aged 40–75 with DM and LDL-C 70–189 mg/dL, and (4) patients aged 40–75 with 10-year ASCVD risk ≥7.5 %, as calculated by pooled cohort equations (http://my.americanheart.org/professional/StatementsGuidelines/Prevention-Guidelines_UCM_457698_SubHomePage.jsp) [9].

In contrast, the NLA, International Society for Atherosclerosis, Canadian Cardiovascular Society, and other organizations still focus on attaining specific lipid targets [1, 13, 14]. NLA recommends the use of

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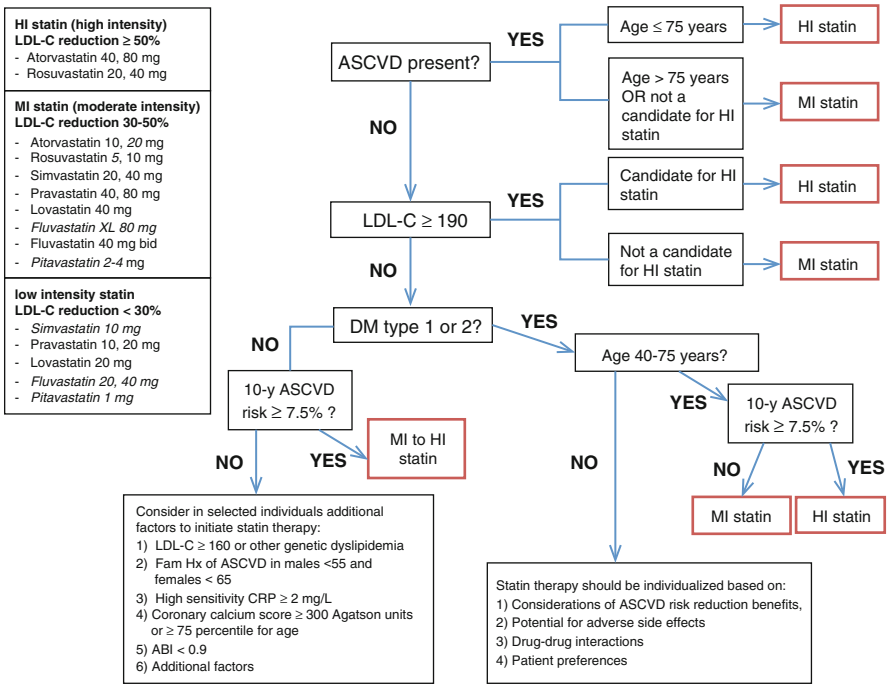

Fig. 1 Algorithm of major recommendations for statin therapy for ASCVD prevention based on 2013 ACC/AHA guidelines. Heart healthy lifestyle is the foundation for prevention. In individuals aged 40–75 without ASCVD, without DM, and with LDL-C 70–189 mg/dL, pooled cohort equations should be used to recalculate risk every 4–6 years. Initial evaluation prior to initiation of statin therapy should include fasting LP, ALT, A1C (if DM status is unknown), and CK (if indicated) and possible evaluation for secondary causes of dyslipidemia. TG ≥500 mg/dL and unexplained ALT elevation >3 × the upper limit of normal should be further evaluated and treated. Patients with LDL-C ≥190 should be evaluated for secondary causes. If dyslipidemia is primary, family should be screened for FH. Adherence to therapy should be tested initially by fasting LP in 4–12 weeks, thereafter every 3–12 months. Lack of anticipated response with good adherence may require increase of statin intensity and/or consider adding non-statin therapy. Statin intolerance requires considering non-statin therapy. In the table showing statin doses for different intensities of therapy, italic font means particular doses or statins were not tested in RCTs

pooled cohort equations, as well as Reynolds or Framingham scoring for risk assessment, in order to establish desired goals. NLA recommends the use of non-HDL-C as the primary target of therapy. In low-, moderate-, and high-risk patients, the non-HDL-C goal is <130 mg/dL (LDL-C goal <100 mg/dL, ApoB goal <90 mg/dL), while in very high-risk patients, the non-HDL-C goal is <100 mg/dL (LDL-C goal <70 mg/dL, ApoB goal <80 mg/dL). Decreased HDL-C (<40 mg/dL in men and <50 mg/dL in women) is not considered a target of therapy, but a marker of cardiovascular risk. TG >500 mg/dL are treated to prevent pancreatitis. TG 150–500 mg/dL is are not a target of therapy, but a marker of cardiovascular risk [1].

3.1 Therapeutic Lifestyle Modifications (TLMs)

TLMs constitute the foundation of management of dyslipidemias. Moderate aerobic physical activity 30–45 min at least 5 × per week improves CV health, leading to decrease in TG and LDL-C, with increase of HDL-C. 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 type I and V dyslipidemias require very low-fat diets [2, 3].

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3.2 Medications

There are various classes of drugs used to treat dyslipidemias (Table 1). 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 upregulation of liver LDL receptors. Statins decrease LDL-C (18–55 % reduction), non-HDL-C (15–51 %), and TG (7–30 %), while increasing HDL-C (5–15 %). They also exert additional pleiotropic effects, unrelated to LDL-C lowering (e.g., anti-inflammatory, antithrombotic, and plaque stabilizing). Their benefits have been confirmed in multiple RCTs.

Statins are generally well tolerated, but up to 10 % of patients may show statin intolerance. Choice of different statins is mostly based on their potency, side effects, drug interactions, and cost (Table 1). 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

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	$–$$	CYP3A4 metabolized, short half-life, avoid erythromycin, azoles, protease inhibitors, cyclosporine, and grapefruit juice. Best absorbed with food	X
Pitavastatin (Livalo)	1 mg qd 4 mg qd	32–46	$$$$	Minimal CYP2C9 and 2C8, long half-life	X
Pravastatin (Pravachol)	10 mg qhs min 80 mg qhs max	25–32 17–32	$–$$	Minimal CYP metabolism, short half-life, avoid erythromycin	X
Simvastatin (Zocor)	10 mg qhs min 40 mg qhs max	27–32 38–43	$–$$	CYP3A4 metabolized, short half-life, avoid erythromycin, azoles, protease inhibitors, cyclosporine, and grapefruit juice. Decrease dosing of diltiazem, verapamil, amlodipine, and amiodarone	X
Cholesterol absorption inhibitors					
Ezetimibe (Zetia)	10 mg qd	20	$$$$	Well tolerated; when combined with statin, it can raise LFTs and contribute to myalgia/myopathy. Available in combination with simvastatin (Vytorin) and atorvastatin (Liptruzet)	C
Bile acid sequestrants					
Colestipol (Colestid)	2–16 g qd or divided (start low and titrate up)	10–25	$$	Do not use when TG >300; constipation; decreased absorption of many drugs and vitamins. Contraindicated when hx of bowel obstruction	B

(*continued*)

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Table 1 (continued)

Medication	Dose range	LDL reduction (%)	Cost	Side effects and special considerations	Pregnancy category
Cholestyramine (Questran)	4–16 g divided bid (start low and titrate up)	10–25	$$	Do not use when TG >300; constipation; decreased absorption of many drugs and vitamins. Contraindicated when hx of bowel obstruction	C
Colesevelam (Welchol)	3.75 g qd or divided bid	10–25	$$$	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 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
ω3 polyunsaturated fatty acids					
DHA/EPA (Lovaza)	4 g qd or 2 g BID	increase up to 40 %	$$$	Well tolerated, may increase ALT, may increase bleeding time	C
EPA (Vascepa)	2 g BID	0	$$$	Well tolerated, may increase ALT, may increase bleeding time	C
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

(*continued*)

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Table 1 (continued)

Medication	Dose range	LDL reduction (%)	Cost	Side effects and special considerations	Pregnancy category
ApoB antisense oligonucleotide					
Mipomersen (Kynamro)	200 mg Subq injection, q week	40–50	$$$$$$$	Use restricted to hoFH, REMS required; risk of hepatotoxicity	B
PCSK9 inhibitor antibodies					
Alirocumab, evolocumab, bococizumab, and others	75–200 mg Subq injection q2 weeks or q month	49–51 %	$$$$?	In phase 3 trials, likely to be on the market soon. Alirocumab reported 54 % RRR in CV events vs. placebo	?

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 very rarely if at all cause liver disease/failure. Liver disease is not a contraindication of their use. 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 [13, 15].

According to 2013 ACC/AHA recommendations, treatment with statins aims for a >50 % reduction of LDL-C with high-intensity statins and >30 % reduction with moderate-intensity statins. When following NLA recommendations, achieving the non-HDL-C goal (representing LDL-P) <130 mg/dL or <100 mg/dL (very high-risk patients) becomes more important.

Statin-intolerant patients, as well as patients who fail to achieve goals on statins alone, can benefit from add-on therapy, such as the intestinal cholesterol absorption blocker ezetimibe (LDL-C reduction of 13–20 %, non-HDL reduction 14–19 %, TG reduction 5–11 %, HDL-C increase 3–5 %) or bile acid sequestrants (LDL-C reduction 15–30 %, non-HDL reduction 4–16 %, HDL-C increase 3–5 %, TG increase up to 10 %).

TG >500 mg/dL are treated with fibrates, niacin, and/or prescription strength omega-3 fish oils (ω3PUFAs), which lower TG 20–50 %. Niacin also lowers LDL-C (5–25 %) and non-HDL-C (8–23 %), raises HDL-C (15–35 %), and decreases LDL-P. European guidelines recommend niacin to lower Lp(a) in patients with levels >50 mg/dL [8]. Fibrates and high-dose ω3PUFAs decrease LDL-P as reflected by the non-HDL decrease 5–19 %, while they either do not affect LDL-C (TG <400 mg/dL) or increase LDL-C 20–25 % (TG >400 mg/dL). Fibrates do increase HDL-C 10–20 %, while the effect of ω3PUFAs on HDL-C is variable.

CETP inhibitors (torcetrapib, dalcetrapib, etc.) were once promising drugs, which failed in clinical trials: they either caused increased mortality or lack meaningful effects despite raising HDL-C levels. An emerging therapy, likely soon to be approved by the FDA, is the use of monoclonal antibodies binding PCSK9. Blocking PCSK9 increases the number of LDL receptors and therefore LDL-P clearance. New drugs approved for hoFH patients include mipomersen and lomitapide, which by different mechanisms prevent VLDL-P synthesis in the liver [2, 3].

3.3 LDL Apheresis

In severe hoFH, often multiple drugs are used to achieve the therapeutic goal of lowering LDL-C at least 50 %. When maximally tolerated pharmacotherapy fails (LDL-C >200 mg/dL in subjects with CAD,

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>300 mg/dL in those without CAD), patients are 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 [1, 7].

3.4 Diet Supplements

Red rice yeast contains natural lovastatin (2–10 mg). However, red rice yeast produced in the USA may not contain any lovastatin, as mandated by the FDA. Plant sterols/stanols lower LDL-C by 5–20 %. Soluble dietary fiber lowers LDL-C by 5–10 %. Soy protein has a marginal benefit on lowering LDL-C. There is no 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. Statins lower CoQ10 levels; therefore, CoQ10 supplementation may prevent myalgias associated with statin use [2, 3, 14].

3.5 Referrals

Difficult to manage patients with dyslipidemias, especially patients with extreme LDL-C and TG elevations, and those who do not respond appropriately to therapy should be referred to clinical lipidologists. This is an emerging subspecialty, open to family physicians (http://www.lipidboard.org).

4 Prevention

Physical activity, weight loss, and a diet low in cholesterol and saturated fat (for patients with high LDL-C) and/or carbohydrates (for patients with atherogenic dyslipidemia) form the basis of prevention of secondary dyslipidemias [2, 3].

5 Family and Community Issues

Cascade screening of family members is advised, especially in the case of FH and elevated Lp(a). 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 (http://thefhfoundation.org).

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Diabetes Mellitus

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Diabetes mellitus (DM) affects over 29 million individuals or 9.3 % of the United States (US) population. Twenty-one million are diagnosed; 8.1 million are undiagnosed. Estimated total costs of diabetes in the US in 2012 were $245 billion, with $176 billion in direct costs and $69 billion in indirect costs. Prediabetes affects 37 % of the US population and 51 % of individuals over age 65 years. The most prevalent form of DM, type 2 DM, has racial preponderances, female predilection, and strong associations with obesity. The rates of type 2 DM in individuals under aged 20 years is increasing especially in minority populations [1]. Published national and international standards of care have been disseminated directly to patients and physicians, heightening the importance of adequate care and glycemic control to minimize devastating long-term complications [2, 3]. Table 1 describes diagnostic criteria for diabetes mellitus and impaired glucose tolerance [4].

Heightened clinical awareness of the genetics and predisposing factors should foster early diagnosis and adequate metabolic control of the type 2 patient. In contrast, the type 1 DM patient generally presents with a more precipitous clinical picture of ketoacidosis. Declining islet β-cell secretory function is more gradual, however, and can evolve over a 10-year period. Occasionally, there is diagnostic confusion owing to a lack of a family history, the absence of significant ketosis, and the absence of significant obesity and other diagnostic hallmarks. The measurement of C-peptide levels, glutamic acid decarboxylase antibodies (GAD), islet cell antibodies, and insulin autoantibodies provides useful diagnostic clarification. C-peptide is the fragment produced when proinsulin, produced by the islets of Langerhans, is cleaved to produce insulin. For every molecule of insulin produced, a molecule of C-peptide has to exist; therefore, C-peptide is a marker of endogenous insulin production. Measurement of a C-peptide level is very useful in documenting insulin secretory capacity in the insulin-treated individual, in whom an insulin level would measure both endogenous and exogenous insulin. Careful clinical follow-up can clarify evolving absolute insulin deficiency even in the absence of these laboratory markers. Latent autoimmune diabetes of adulthood (LADA) is characterized by positive GAD antibodies and has a more indolent nature. Patients may remain on non-insulin-based pharmacotherapy for years before requiring insulin therapy [5].

Pathophysiology

Previously, type 1 DM was considered to be an acute event. Viral associations were invoked with regard to the seasonal trends in its incidence. However, patients can have markers of islet destruction in the form of GAD antibodies, islet cell antibodies, and/or insulin autoantibodies for up to 10 years prior to the development of overt DM. Positive antibodies along with the loss of first-phase insulin secretion in response to an intravenous glucose tolerance test are highly predictive of evolving type 1 DM. Immunomodulation in type 1 DM with immunosuppressive or stem cell therapy has proved elusive despite studies demonstrating short-term success.

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Table 1 Diagnostic criteria for diabetes mellitus, impaired glucose tolerance, and gestational diabetes

Nonpregnant adults
Criteria for diabetes mellitus: diagnosis of diabetes mellitus in nonpregnant adults should be restricted to those who have one of the following
Fasting plasma glucose ≥126 mg/dl. Fasting is defined as no caloric intake for at least 8 h
Symptoms of diabetes mellitus (such as polyuria, polydipsia, unexplained weight loss) coupled with a random plasma glucose level of ≥200 mg/dl. Random is defined as any time of day without regard to time interval since the last meal
2-h postprandial plasma glucose ≥200 mg/dl during an oral glucose tolerance test. The test should be performed by World Health Organization criteria using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water
Hemoglobin A1c (HbA1c) ≥ 6.5 % by a National Glycosylated Hemoglobin Standardization Program (NGSP)-certified or traceable method
Note: In the absence of unequivocal hyperglycemia with acute metabolic decompensation, these criteria should be confirmed by repeat testing on a second occasion. The oral glucose tolerance test is not recommended for routine clinical use
Criterion for impaired glucose tolerance: 2-h postprandial plasma glucose ≥140 mg/dl and ≤199 mg/dl during an oral glucose tolerance test. The test should be performed by World Health Organization criteria using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water
Pregnant women – see chapter "12"

In contrast, type 2 DM is associated with genetic predispositions, advancing age, obesity, and lack of physical fitness. The importance of appropriate caloric intake and energy expenditure has been clearly established. The Twin Cycle Hypothesis of glucose and lipid defects involves lipid accumulation in the liver and worsening hepatic insulin resistance. Additionally, lipid accumulation in the β-cell worsens β-cell function and promotes β-cell apoptosis. Hence, caloric restriction will reduce hepatic and β-cell lipid accumulation [6]. Although type 2 DM is a syndrome of insulin resistance and β-cell secretory defects, in any given individual it is not possible to define the degree of insulin resistance versus secretory defects with any precision. The earliest metabolic defect found in first-degree relatives of individuals with type 2 DM is defective skeletal muscle glucose uptake with later increased insulin resistance at the level of the liver and resultant uncontrolled hepatic glucose output. The ensuing hyperglycemia can have a toxic effect called glucotoxicity on the islets, resulting in worsening secretory defects with declining insulin secretion and self-perpetuating hyperglycemia. Hyperglycemia can also downregulate glucose transporters. To become hyperglycemic, insulin secretion must be insufficient to overcome the insulin resistance; it has been estimated that insulin secretory capacity is reduced by 50–80 % at the time of diagnosis of type 2 DM. It is unclear whether secretory defects or insulin resistance is the primary defect even for type 2 DM. Patients may exhibit many abnormalities, including loss of first-phase insulin secretion and loss of the pulsatility of insulin secretion. Additionally, both men and women tend to have abdominal obesity, which is associated with hyperinsulinemia and insulin resistance. Type 2 DM is a syndrome not only of disordered glucose metabolism but also of lipid metabolism; many patients have a concurrent dyslipidemia manifesting as elevations in serum triglycerides, reductions in high-density lipoprotein (HDL) cholesterol, and marginal increases in total cholesterol. This dyslipidemia results from uncontrolled hepatic very low-density lipoprotein (VLDL) secretion and defective clearance of lipoprotein molecules. The associations of hyperinsulinemia and insulin resistance with essential hypertension are well documented along with the marked tendency for patients with essential hypertension to develop DM and the converse – patients with type 2 DM developing essential hypertension. A central unifying hypothesis focuses on hyperinsulinemia and insulin resistance being primary metabolic aberrations that result not only in hyperglycemia but also hypertension and dyslipidemia. Defronzo's original triumvirate of liver, β-cell, and skeletal muscle dysfunction has been expanded and replaced by the concept of the ominous octet which is now regarded as the basis of the pathophysiology of type 2 DM [7]

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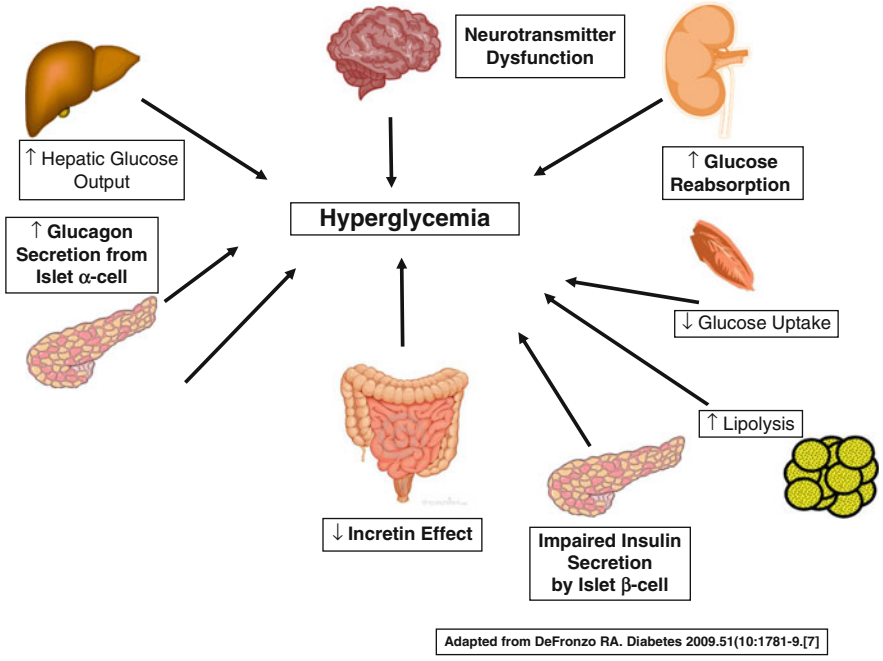

Fig. 1 The ominous octet (**Adapted from DeFronzo [7]**)

(see Fig. 1). Other aspects of the cardiometabolic syndrome include polycystic ovarian syndrome (PCOS), obstructive sleep apnea, and hyperuricemia [8].

Importance of Glycemic Control

The Diabetes Control and Complications Trial (DCCT) in individuals with type 1 DM proved the profound impact of intensive therapy on reducing the risk of microvascular complications. The EDIC trial (Epidemiology of Diabetes Intervention on Complications), the extension of the DCCT through 18 years, has continued to demonstrate that prior good glycemic control provided reduced future risk of microvascular and macrovascular complications – the concept termed "metabolic memory"[9]. A potential negative aspect of attempts to achieve optimum glycemic control by intensive insulin therapy is the potential for severe hypoglycemia. An educated and motivated patient working with a multidisciplinary healthcare team can significantly reduce the risk of this. Glycemic goals may need to be modified in the individual with poor hypoglycemia awareness. The United Kingdom Prospective Diabetes Study (UKPDS), a 20-year prospective study in newly diagnosed type 2 DM patients, demonstrated that both intensive glycemic control and intensive blood pressure control reduced the risk of microvascular and macrovascular complications of DM. The 10-year follow-up of the UKPDS showed reduced complications from earlier good glycemic control, a concept that was termed the "legacy effect"[10]. Excellent metabolic control is defined by normal hemoglobin A1c (HbA1c) levels without significant hypoglycemia as an achievable goal.

Defining Control

The definition of DM control has varied throughout the decades. The HbA1c, the marker of long-term glycemic control, measures the degree of glycosylation of the A1c subfraction of hemoglobin and reflects

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the average blood glucose over the preceding 60–90 days. The HbA1c allows for identification of possible patient falsification of, or errors in, home blood glucose monitoring (HBGM) results. It is a useful motivating tool for patients; it often becomes a perceived challenge to reduce the result within the constraints of hypoglycemia. The National Glycosylated Hemoglobin Standardization Program (NGSP) is responsible for standardizing and correlating various assays to the DCCT methodology. Hemoglobinopathies can skew HbA1c results and can be detected via inspection of the chromatograms in the laboratory. The American Diabetes Association recommends that the HbA1c be performed at least two to four times per year in all patients. Given that the DCCT demonstrated a linear relation between the HbAlc (all the way into the normal, nondiabetic range) and microvascular complication risk, the ideal is therefore normalization of the HbA1c within the constraints of hypoglycemia. The Action to Control Cardiovascular Risk Reduction (ACCORD) study in individuals with type 2 DM of 10 years duration and preexisting cardiovascular disease however showed increased cardiovascular events and mortality in the intensively treated group [11]. This increase is believed by many experts to be due to the hypoglycemia risks with the use of insulin and other secretagogues in this high-risk population. A recent meta-analysis showed a disturbing association between sulfonylurea/insulin combination and cardiovascular risk and mortality [12]. Measurement of 1,5 anhydroglucitol reflects glucose control in postprandial states but is typically utilized in research settings as opposed to use in clinical practice. Fructosamine assays as a marker of glycemic control over the preceding 2–3 weeks are rarely used in clinical practice.

Glycemic Goals

Glycemic goals should be individualized based upon age, diabetes duration, complications of diabetes, comorbid conditions, and life expectancy. The ADA's goals are for most nonpregnant adults to have an HbA1c <7.0 % (with a view to <6.5 % in selected individuals) and <8.0 % in less healthy individuals. ADA's preprandial capillary glucose goal is 80–130 mg/dl with peak postprandial capillary glucose goal of <180 mg/dl [13]. The American Association of Clinical Endocrinologists (AACE) recommends tighter glycemic goals of an HbA1c <6.5 % for most individuals with less stringent goals for less healthy individuals such as those with a limited life expectancy. AACE's glycemic goals are a fasting plasma glucose <110 mg/dl with 2-h postprandial goals <140 mg/dl [3].

In addition to markers of glycemic control, it is critical to monitor other clinical parameters. Annual lipid profiles are an integral part of overall DM care in view of the high prevalence of dyslipidemia especially in the patient with type 2 DM. In type 1 DM patients, lipid disturbances are uncommon unless patients are in poor glycemic control, have a familial dyslipidemia, or have renal insufficiency. Markers of nephropathy are also important to measure. The earliest marker, microalbuminuria, is not only a forerunner of overt clinical nephropathy but is also a marker for greatly increased cardiovascular risk in both type 1 DM and type 2 DM patients. Microalbuminuria can be conveniently measured in spot urine specimens or by an overnight albumin excretion rate, rather than the more cumbersome 24-h urine collection.

Patient Education

Patient attention to management principles decidedly affects short-term metabolic control and ultimately has an impact on long-term complications. Interactions of patients with registered nurses and dietitians (preferably certified diabetes educators) are critical. The presence of family members and significant others during the educational sessions is vital to a successful outcome. Education must encompass a

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comprehensive understanding of the pathophysiology of DM and its complications and the importance of attaining and sustaining metabolic control.

Home Blood Glucose Monitoring

Accurate HBGM is a key to successful diabetes management. In type 1 DM patients, the minimum safe and efficacious schedule is premeal and *hs*. For optimum safety and efficacy, individuals should also monitor BG levels 2-h postprandially and prior to driving. Periodic overnight monitoring is also helpful to assess nocturnal glycemic issues. In individuals with type 2 DM, performing HBGM daily at varying times of the day is a good start. Pending the pharmacotherapy regimen, individuals with type 2 DM may need to monitor BG levels up to that ideally recommended for the individual with type 1 DM. Results stored in the memory of meters can be downloaded to a computer via a meter-specific computer program. However, the traditional written log actually provides more information when an educated, motivated patient records HBGM results, times of day, medication administered, carbohydrate intake, and notes regarding activity and other variables.

Continuous glucose sensors which measure interstitial glucose levels are approved by the US Food and Drug Administration for trend detection only and do not replace HBGM for insulin dosing or for confirmation of hypoglycemia. Calibrations must be done at least every 12 h and should ideally be performed when glucose levels are in steady state (fasting or 3–4 h postprandially) to ensure best correlation. One insulin pump has a "threshold suspend" feature whereby when the individual's interstitial glucose level reaches a predefined glucose level, the insulin pump will suspend insulin delivery.

Medical Nutrition Therapy

Education must also focus on dietary principles. Many patients still perceive that "sugar-free" implies carbohydrate-free and that "sugar-free" foods cannot affect blood glucose control. This belief fails to recognize the monomer/polymer concept and the fact that carbohydrates are ultimately digested into glucose. Achieving a high degree of dietary education generally requires several sessions with a dietitian/nutrition specialist. Dietary principles are an ongoing exercise, and eradication of myths and misconceptions is a major task.

For individuals with diabetes, the macronutrient distribution must be individualized although the total dietary fat intake should be 20–30 % of kcal. Caloric requirements are based on ideal body weight (IBW) – not actual body weight [14]. We calculate IBW by the Hamwi formula.

Women
100 lb for 5 ft
5 lb for every additional inch
Example: woman $5'3'' = 115$ lb IBW
Men
106 lb for 5 ft
6 lb for every additional inch
Example: man $5'8'' = 154$ lb IBW

Based on anthropometric measures, 10 % may be subtracted or added based on small body frame or large body frame, respectively.

Basal caloric requirements can then be calculated as follows.

$$\text{Woman } 5'3'' : \text{IBW} = 115 \text{ lb}$$
$$115 \times 10 \text{ kcal} = 1,150 \text{ kcal/day}$$

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Add 300–400 kcal/day for moderate to strenuous activity. Subtract 500 kcal/day to achieve 1 lb per week of weight loss.

Because individuals with DM type 2 are generally hyperinsulinemic, diet prescriptions for weight loss and maintenance require a lower caloric level than previously mentioned. The activity factor in kilocalories (300–400 kcal/day) can be modified in these individuals. For the overweight type 2 DM patient, caloric restriction is of major importance. A hypocaloric meal plan that is acceptable to the patient, regardless of the macronutrient composition, is the key [15]. Patients tend to underestimate caloric intake and overestimate energy expenditure. Consumption of an extra 100 kcal daily over and above metabolic needs, which seems trivial, will result in a 10 lb weight gain over 1 year; conversely, subtraction of 100 kcal daily will result in a 10 lb weight loss over 1 year. In individuals with type 2 DM, the Look AHEAD trial showed a reduction in HbA1c with diet and exercise [16] equivalent to many forms of pharmacotherapy.

In contrast, diet for the type 1 DM patient should involve careful counting of carbohydrate grams via weighing and measuring food and accurate matching of rapid-acting analog insulin (RAA) to carbohydrate planned to be consumed. In addition to precise carbohydrate gram counting to match RAA insulin to planned carbohydrate intake, patients must learn about carbohydrate augmentation for physical activity. Patients also need instruction on carbohydrate strategies for dealing with intercurrent illness when the usual complex carbohydrate may be substituted with simple carbohydrate. Although it has long been said that diet is the cornerstone of DM management, effective DM dietary education is still problematic owing to time constraints and reimbursement problems.

Exercise

Aerobic exercise combined with resistance training can have a profound beneficial effect on diabetes control. The benefits of exercise include improved control of glucose, lipids, and blood pressure; improved cardiorespiratory capacity; reduction in body fat with an increase in muscle mass; reduced fall risk; and an overall increase in well-being. Exercise needs to be tailored to each individual's physical capacity, DM complications, comorbid medical conditions, and personal preferences regarding the type of exercise and location. Exercise needs to become a priority rather than an option. An easy start can be wearing a pedometer and walking with a view to reach the ADA's goal of 10,000 steps per day. The ultimate goal is engaging in aerobic exercise 5 days per week for 45 min daily.

Insulin

Insulin-treated patients must be aware of the many facets of insulin therapy. The use of insulin pen devices has replaced the traditional vial and syringe for most individuals; however, many insulin users fail to follow manufacturers' recommendations for "the 2-unit air shot" prior to each insulin injection. Site selection, consistency, and rotation remain crucial. Insulin absorption is most rapid from the upper abdomen; the arms, legs, and buttocks, respectively, are next. We find that administering the premeal RAA insulin in the abdomen optimizes postmeal control. In contrast, the buttocks, as the slowest absorption site, is not a good choice for premeal injections. However, the lower buttocks is an ideal site for bedtime injections of the intermediate-acting insulin [neutral protamine Hagedorn (NPH)] to minimize nocturnal hypoglycemia in patients still using this less physiologic insulin. Haphazard site selection and rotation can lead to erratic glycemic control. Because of the variability in absorption among sites, we suggest site consistency – using the same anatomic site at the same time of day (all breakfast injections in the abdomen, all dinner injections in the arms, all bedtime injections of NPH in the lower buttocks). Broad rotation within the sites is important to eliminate local lipohypertrophy which is less common with the use of human analog insulins. Injecting into lipohypertrophic sites delays the absorption of insulin. The RAAs with earlier peaks at 60–90 min postinjection improve postprandial glycemic control. This facilitates

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insulin injection timing as it is injected 0–10 min premeal. In contrast, regular insulin requires premeal timing of insulin injections (generally at least 30 min) to optimize postprandial glycemic control, as its peak effect is 2–3 h after injection. Patients need a comprehensive perspective on insulin adjustments for hyperglycemia, altered physical activity, illness management, travel, and alcohol consumption.

Patients need education on the pathophysiology, prevention, and treatment of microvascular complications. Education on macrovascular risk factors and their modification for prevention of cardiovascular, cerebrovascular, and peripheral vascular disease is also critical. Patients can have a considerable impact on decreasing foot problems and amputations with simple attention to hygiene (avoidance of foot soaks), daily foot inspection, and the use of appropriate footwear. These measures can greatly reduce the incidence of trauma, sepsis, and ultimately amputations.

Diabetic Complications

Complications of DM include those that are specific to DM and those that are nonspecific but are accelerated by the presence of DM. The microvascular complications of DM are diabetes specific – the triad of retinopathy, neuropathy, and nephropathy. Macrovascular disease – atherosclerosis – a common complication in patients with DM, is not specific to DM but is greatly accelerated by its presence. A major misconception among patients and even physicians is that the complications of DM tend to be less severe in patients with type 2 DM. Patients with type 2 DM or impaired glucose tolerance have greatly accelerated macrovascular disease and also suffer significant morbidity from microvascular complications.

Retinopathy

Retinopathy, the commonest cause of new-onset blindness during middle life, is broadly classified as nonproliferative (background) and proliferative. Macular edema is characterized by the collection of intraretinal fluid in the macula, with or without lipid exudates (hard exudates). In nonproliferative retinopathy, ophthalmoscopic findings may include microaneurysms, intraretinal hemorrhages, and macular edema. In more advanced nonproliferative retinopathy, cotton wool spots reflecting retinal ischemia can be noted. In proliferative retinopathy, worsening retinal ischemia results in neovascularization, preretinal or vitreous hemorrhage, and fibrous tissue proliferation. Macular edema can also occur in proliferative retinopathy. Early diagnosis and treatment with laser therapy has been shown to be vision sparing in patients with macular edema and/or proliferative retinopathy. Treatment with injectable anti-vascular endothelial growth factor (VEGF) products has been demonstrated to reduce hemorrhage and macular edema. Studies clearly document the importance of annual examinations by an ophthalmologist for all patients. The use of optical coherence tomography (OCT) to assess retinal thickness enhances diagnosis and treatment of retinal disease. Good visual acuity does not exclude significant retinal pathology; unfortunately, many patients, and healthcare providers alike, believe good visual acuity implies the absence of significant retinal disease.

Neuropathy

Diabetic neuropathy is discussed in chapter “74.”

Nephropathy/Hypertension

Diabetic nephropathy first manifests as microalbuminuria, detected by a spot urine microalbumin-to-creatinine ratio or by an elevated timed overnight albumin excretion rate. The presence of microalbuminuria should alert the patient and physician to the need for stringent glycemic control; such

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control has been shown to decrease the progression from microalbuminuria to clinical proteinuria and attendant evolution of hypertension. Hypertension increases the rate of deterioration of renal function in patients with DM, and aggressive treatment is mandatory. The Captopril Diabetic Nephropathy Study demonstrated that treatment with the angiotensin-converting enzyme inhibitor (ACEi) captopril was associated with a 50 % reduction in the risk of the combined end points of death, dialysis, and transplantation in macroproteinuric (>500 mg/24 h) type 1 DM patients. Overall, the risk of doubling the serum creatinine was reduced by 48 % in captopril-treated patients. The beneficial effects were seen in both normotensive and hypertensive patients such that captopril at a dose of 25 mg po tid is approved for use in normotensive proteinuric (>500 mg/24 h) type 1 DM patients [17]. In light of this and other studies in both type 1 and type 2 DM patients, the use of ACEI for prevention of progression of microalbuminuria and macroalbuminuria is recommended, unless there is a contraindication. For antihypertensive therapy, ACEi is the antihypertensive of choice, unless contraindicated, given the data not only in nephropathy but also in retinopathy.

Given the macrovascular benefits alone, we should probably be looking for reasons not to prescribe ACEis in individuals with type 2 DM, rather than reasons to prescribe them. In patients intolerant of ACEis due to cough, angiotensin receptor blockers (ARBs) are good alternative. The use of prophylactic ACEis or ARBs in normotensive normoalbuminuric individuals with type 1 DM is not justified by clinical trial data. Calcium channel blockers are good alternatives in light of data that show decreasing proteinuria with many of these agents over and above that achievable with conventional antihypertensive therapy. Avoidance of excessive dietary protein intake is also important, as excessive dietary protein may be involved in renal hypertrophy and glomerular hyperfiltration.

Patients with DM in general are salt sensitive, having diminished ability to excrete a sodium load with an attendant rise in blood pressure; therefore, avoidance of excessive dietary sodium intake is important. Hyperinsulinemia and insulin resistance are also important in the genesis of hypertension, with insulin-resistant patients having higher circulating insulin levels to maintain normal glucose levels. Associated with this insulin resistance and hyperinsulinemia is the occurrence of elevated blood pressures even in nondiabetic individuals. Insulin is antinatriuretic and stimulates the sympathetic nervous system; both mechanisms may be important in the genesis of hypertension. Hypertension exacerbates retinopathy, nephropathy, and macrovascular disease and must be diagnosed early and managed aggressively. When lifestyle modifications fail to control blood pressure, the pharmacologic agent chosen should be not only efficacious but kind to the metabolic milieu. The ACCORD blood pressure trial showed no cardiovascular risk reduction benefit in achieving the epidemiologic ideal blood pressure of 115/75 mmHg versus 130/80 mmHg [18]. Monotherapy of hypertension is frequently unsuccessful, especially in the setting of nephropathy, such that combination therapy is frequently needed with special attention to underlying concomitant medical problems (see chapter “77”).

Diuretics are very useful in edematous states. Beta-blockers have an important role in the post-myocardial infarction/anginal patient and in the heart failure patient. The benefits of beta-blockade in these patients outweigh the theoretical problems of masking of hypoglycemia, delay in recovery of hypoglycemia, and the worsening of insulin resistance. ACEIs or angiotensin receptor blockers (ARBs) are generally the preferred initial antihypertensive therapy in individuals with DM; calcium channel blockers are a good choice for the angina patient. Alpha-blockers are a good choice in the patient with benign prostatic hyperplasia; however, they are generally not used as monotherapy given the data suggesting increased risk of congestive heart failure. Coadministration of aliskiren (Tekturna) with ACEis or ARBs is contraindicated based on the Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Endpoints (ALTITUDE). The results demonstrated similar systolic and diastolic blood pressure control with an increased risk of significant hyperkalemia and hypotension in the aliskiren-treated patients [19].

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Macrovascular Disease

Macrovascular disease is the major cause of premature death and considerable morbidity in individuals with DM, especially those with type 2 DM. Conventional risk factors for macrovascular disease warrant special attention in DM; they include smoking, lack of physical fitness, excessive dietary fat intake, obesity, hypertension, and hyperlipidemia. Smoking cessation and appropriate antiplatelet therapy are important. Correction and control of hyperlipidemia through improved metabolic control and the use of diet or pharmacotherapy are mandatory for the DM patient. LDL cholesterol lowering has been demonstrated to confer greater coronary event risk reduction and mortality reduction in diabetic patients than in nondiabetic patients. DM is one of the few diseases in which women have greater morbidity and mortality than men, especially in terms of macrovascular disease, with African-American women bearing the greatest load. There are now two competing guidelines in regard to lipid therapy. The Adult Treatment Panel III guidelines [20], which are most familiar to clinicians, were developed based on the analysis of many decades of research (randomized clinical trials, epidemiologic trials, in vivo studies, and in vitro studies) and focus on the atherogenicity of lipoproteins and utilize goal low-density lipoprotein (LDL-C) targets. In contrast, the American College of Cardiology/American Heart Association ATP IV, based only on randomized clinical trial evidence, does not utilize LDL goals and in fact focuses solely on the use of the drug class of statins in various populations [21]. These new guidelines result in many more individuals being recommended for statin treatment. They are more cumbersome in application and do not provide information on monitoring safety and efficacy [22]. A meta-analysis of high-dose versus moderate-dose statin therapy showed that high-dose statin therapy was associated with increased risk of new-onset type 2 DM. However, moderate-dose therapy conveyed less cardiovascular protection [23]. The ACCORD trial demonstrated that routine use of fibrates is not justified [24]. The use of extended-release niacin for increasing high-density lipoprotein (HDL-C) and reducing triglyceride levels remains controversial in terms of reducing cardiovascular events without untoward side effects [25]. Extended-release niacin may still be beneficial in selected patients [26].

Foot Problems

Foot problems in the diabetic are a major cause of hospitalization and amputations. They generally constitute a combination of sepsis, ischemia, and neuropathy. The presence of significant neuropathy facilitates unrecognized repetitive trauma without appropriate pain that can result in ulceration and ultimately nonhealing. Additionally, neuropathy may mask manifestations of peripheral vascular disease (PVD) (e.g., claudication and rest pain) such that patients may have critical ischemia with minimal symptoms. Therefore, PVD may be difficult to diagnose on the usual clinical grounds alone. Not only may neuropathy mask clinical symptoms, the clinical signs may be somewhat confusing. Patients with less severe neuropathy may exhibit cold feet related to arteriovenous shunting, and patients with more severe neuropathy may exhibit cutaneous hyperemia related to autosympathectomy. Noninvasive vascular testing along with clinical evaluation is helpful for the diagnosis and management of PVD. Calcific medial arterial disease is common and can cause erroneously high blood pressure recordings in the extremities, confusing the assessment of the severity of PVD. Severe ischemia with symptoms and nonhealing wounds generally requires angioplasty/stenting or formal surgical intervention. Milder symptoms and disease may respond favorably to enhanced physical activity and the use of one of the hemorheologic agents – pentoxifylline (Trental) or cilostazol (Pletal). Appropriate podiatric footwear and management are important to both ulcer healing and prevention of repetitive trauma. Early PVD can readily be detected by ankle-brachial indices using a handheld Doppler. A reduced ankle-brachial index at the posterior tibial artery in isolation has been demonstrated to be an important marker for PVD and also confers a 3.8-fold increased risk of cardiovascular death.

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Achieving Glycemic Control

Type 1 DM

Optimal management of type 1 DM requires an educated, motivated patient and a physiologic insulin regimen. The major challenge is physiologic insulin replacement matched to dietary carbohydrate with appropriate compensation for variables such as exercise. The three major factors in glycemic control are carbohydrate intake, insulin, and physical activity. If one variable changes, a second variable must change to compensate. Physiologic insulin replacement is the standard of care and involves intensive insulin basal-bolus therapy with multiple injections or the use of insulin pump therapy. The key to successful insulin therapy is individualization. Several regimens have been utilized to achieve glycemic control. In the individual with type 1 DM, the total daily dose (TDD) is typically 0.5–0.8 units/kg of body weight. However, the TDD can be very low in very insulin-sensitive individuals and in the post-pancreatectomy patient due to glucagon deficiency. Basal insulin requirements are typically between 40 % and 50 % of the TDD. A common mistake is to keep increasing the basal insulin dose to compensate for postprandial hyperglycemia. The net result to this flawed strategy is severe hypoglycemia with delayed meals and weight gain while "eating up" to the basal insulin.

Insulin pump therapy utilizes only RAA insulin and delivers basal insulin in minute amounts every few minutes to control hepatic glucose output and disposal in the fasting state. The rates are preprogrammed in 0.025 unit increments. Insulin pumps have the ability to titrate doses to accommodate individual dawn hormonal surges and activity levels. Pumps also have preprogrammed individualized algorithms for RAA to carbohydrate ratios and correction factors for hyperglycemia. They also have the ability to deliver dual wave boluses which can be used for meals with slowly digested complex carbohydrate and higher fat meals or in cases of gastroparesis. Boluses can be split to deliver a specified percentage for immediate delivery (i.e., 70 %) and then the remainder over a number of hours (i.e., 30 % over 3.5 h).

Modern injection-based regimens revolve around the use of a true basal insulin such as insulin glargine (Lantus), insulin glargine U-300 (Toujeo), or insulin detemir (Levemir) to control hepatic glucose output and disposal in the fasting state. RAA should be injected prior to ingestion of carbohydrate at meals and snacks. Patients need to be educated and engaged in accurate carbohydrate counting for safety and efficacy. Patients need to have established RAA to carbohydrate ratios, such as 1 unit of RAA for every 10 g of carbohydrate to be consumed, so that as the planned carbohydrate intake varies the RAA dose varies. Insulin-sensitive individuals may have a ratio of 1 unit of RAA for every 40 g of carbohydrate, whereas the more insulin-resistant patient, such as a type 1 DM patient with a family history of type 2 DM, may have a ratio of 1 unit of RAA for every 3 g of carbohydrate. Insulin-to-carbohydrate ratios often vary throughout the day with many individuals requiring more insulin at breakfast due to the dawn hormonal surge lasting until 10–11 AM. Timing of RAA injections to 10–15 min premeal/pre-snack optimizes postprandial glycemic control. Routine postprandial RAA administration is discouraged except in such situations as unknown/unpredictable carbohydrate intake as in toddlers, the extreme elderly patient, or in situations of illness. Fixed doses of RAA are typically not useful as individuals do not consume the same amount of carbohydrate at each meal. Patients need to have an insulin algorithm for guidance in administration of additional RAA insulin in response to hyperglycemia. For example, in the individual taking 0.5 units TDD/kg body weight, prior to meals and at bedtime, for every 50 mg/dl elevation in blood glucose above 100 mg/dl, take 1 additional unit of RAA to reduce the blood glucose level by 50 mg/dl. In patients with a lower TDD/kg body weight, the reduction may be 70 mg/dl per additional unit of RAA, while in those taking a higher TDD/kg body weight, the reduction may be 30 mg/dl per additional unit of RAA.

Use of a premixed insulin or split-mixed insulin regimen should be rare for the type 1 DM patient as they are unphysiologic. Such regimens are antiquated and have inherent risks of nocturnal hypoglycemia

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Table 2 Hypoglycemia management strategies

Causes	Signs and symptoms	Treatment
Insulin/secretagogue overdose	Sympathomimetic	Conscious – 15 g
Carbohydrate omission Missed/late meal Missed/late snack	Coldness Clamminess Shaking Diaphoresis Headaches	Simple carbohydrate Juice 4 oz Regular soda 6 oz 3-4 glucose tablets
Uncompensated activity/exercise	Neuroglycopenic Confusion Disorientation Loss of consciousness	Unconscious Glucagon SC[a] D_{50} 50 cm^3 IV

[a]We do not recommend the use of gel products for treatment of unconscious hypoglycemia, as aspiration is a potential hazard

from the pre-supper intermediate-acting insulin when stringent control of the fasting blood glucose is sought. This regimen was one of those used in the conventional group in the DCCT and was inferior at reducing the risk of complications.

Patients also need a plan for RAA/carbohydrate adjustment for physical activity and illness. Many episodes of severe hypoglycemia occur in the context of unplanned physical activity and dietary errors; likewise, many episodes of ketoacidosis occur during episodes of minor intercurrent illness. Physical activity has a major impact on glycemic control. In general, every 20–30 min of physical activity, pending intensity, over the patient's baseline activity level will result in a 50 mg/dl decrement in blood glucose. For physical activity, a proactive reduction in RAA dosage of 1–2 units per 20–30 min of activity generally suffices pending the intensity of the activity. The other option is to augment carbohydrate intake (i.e., 15 g carbohydrate prior to every 20–30 min of activity). It is not recommended to inject RAA into an exercising extremity such as the leg due to enhanced absorption and risks of hypoglycemia. Patients must fully understand that illness is a situation of insulin resistance and that at all of the routine insulin doses should be administered. Carbohydrate from meals and snacks may be substituted as simple carbohydrate in the form of liquids such as juices and regular ginger ale.

Inhaled human insulin (Afrezza inhalation powder) has recently been approved as an alternative to subcutaneous injections of RAA or regular insulin. It must be used in combination with basal insulin. Acute bronchospasm is a risk in patients with asthma or chronic obstructive pulmonary disease and is therefore contraindicated in these patients. A decline in pulmonary function can be seen even in patients without preexisting chronic lung disease. Spirometry should be performed at baseline, at 6 months, and then annually even in patients who exhibit no pulmonary symptoms. Long-term studies of its safety, including cardiopulmonary effects, are pending.

Severe hypoglycemia in the well-educated, adherent, motivated patient on a physiologic insulin regimen is uncommon. Most severe hypoglycemic episodes are explained on the basis of diet, exercise, and/or insulin-adjustment errors. The individual who is attempting to achieve true euglycemia, however, is at risk for periodic easily self-treated hypoglycemia. See Table 2 hypoglycemia for management strategies. For the individual with type 1 DM who has been educated thoroughly, is on a physiologic insulin regimen with carbohydrate counting precision, and has algorithms for illness and physical activity, failure to attain the desired degree of glycemic control is largely related to psychosocial variables or, occasionally, altered and unpredictable insulin kinetics.

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Type 2 DM

In most instances, type 2 DM is a syndrome of insulin resistance coupled with variable secretory defects, both of which can be compounded by glucotoxicity. As insulin resistance is related to genetic factors, obesity, and sedentary lifestyle, the mainstay of treatment for the type 2 DM patient is reduction of insulin resistance through diet and exercise and reversal of glucotoxicity acutely through reestablishment of euglycemia. Many patients still perceive themselves to be more absolutely insulin deficient than insulin resistant and are willing to accept insulin therapy as a compromise in the context of failed weight loss efforts. Additionally, many patients perceive pharmacotherapy to be equivalent to a diet and exercise regimen alone, assuming the desired degree of glycemic control is achieved. Chronic nonadherence to a diet regimen with resultant failure of weight loss or progressive obesity frequently leads to mislabeling the patient as a "brittle diabetic." It is important to avoid premature and unnecessary insulin therapy in these individuals and to stress to them the importance of diet and exercise as the most physiologic approach to controlling their metabolic disorder. Premature insulin therapy can lead to excessive weight gain with resultant progressive increasing insulin doses and a vicious cycle of weight gain, frequently without improvement in glycemic control.

Pharmacotherapy for Type 2 DM

To achieve HbA1c goals, the vast majority of type 2 DM patients will require combination therapy. Pharmacotherapy for type 2 DM should be directed at addressing the pathophysiologic components of the ominous octet [7] (see Fig. 1).

Decreasing Insulin Resistance/Increasing Insulin Sensitivity

Metformin hydrochloride and the thiazolidinediones work via different mechanisms. Metformin mainly inhibits the uncontrolled hepatic glucose production, while the thiazolidinediones mainly enhance skeletal muscle glucose uptake and decrease free fatty acid efflux from adipocytes.

Metformin IR (Glucophage) and metformin ER (Glucophage XR, Glumetza) are true insulin sensitizers, decreasing hepatic glucose production and enhancing peripheral glucose utilization. They are antihyperglycemic and do not stimulate insulin secretion; hence, when used as monotherapy, they cannot induce hypoglycemia. Lipid levels may improve. Ideal candidates for treatment are overweight or obese type 2 DM patients. For a 70 kg man, the usual starting dose is metformin IR 500 mg bid or metformin ER 500 mg qpm; maximum dose metformin IR is 850 mg tid or metformin ER 2,000 mg qpm. In the UKPDS, despite similar levels of glycemic control, the subset of obese type 2 DM patients treated with metformin had a statistically significantly lower cardiovascular event and death rate than the other groups. Thus, metformin must be modulating other aspects of the cardiometabolic syndrome. The potentially fatal side effect of lactic acidosis generally occurs only when metformin is used in contraindicated patients: those with renal insufficiency, liver disease, alcohol excess, or underlying hypoxic states (congestive heart failure, chronic obstructive pulmonary disease, significant asthma, acute myocardial infarction). Metformin should be discontinued in the morning of (1) elective surgery that may require general anesthesia and (2) elective imaging procedures using contrast materials (e.g., intravenous pyelogram, cardiac catheterization) and should not be restarted for 48–72 h after the surgery/procedure, pending documentation of a normal serum creatinine. Adjustments in the patient's diabetes regimen will have to be made for this time period to maintain glycemic control. Metformin is contraindicated in women with a serum creatinine $\geq$1.4 mg/dl, in men with a serum creatinine $\geq$1.5 mg/d, significant hepatic dysfunction, type 1 DM, and acute and chronic conditions associated with hypoxia. Metformin therapy has been associated with malabsorption of vitamin B12; hence, monitoring of vitamin B12 levels is recommended [27]. Metformin should be used as the foundation of pharmacotherapy for type 2 DM assuming no contraindications.

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Metformin can enhance fertility in premenopausal women with PCOS; appropriate contraception should be used to prevent unwanted pregnancy.

Thiazolidinediones [pioglitazone (ACTOS) and rosiglitazone (Avandia)] are antihyperglycemic insulin-sensitizing agents that bind to the peroxisome proliferator-activated receptor (PPAR) and amplify the insulin signal. Insulin levels decline. In addition to glucose-lowering properties, they have purported beneficial effects on the other components of the cardiometabolic syndrome. These agents may also assist in the preservation of β-cell function via reduction in lipid deposition within the islets of Langerhans – a concept called lipotoxicity, a finding documented in animals. There is no hypoglycemia when used as monotherapy. LDL-C concentration rises but with less small dense LDL. Triglycerides decline and HDL-C levels rise. Weight gain can occur with these agents. These agents can be safely used in patients with renal insufficiency without the need for dosage adjustment. A contraindication to their use is liver disease or elevations in hepatic transaminases. Edema is the commonest clinical adverse effect and is worsened by concomitant insulin therapy. Although the risk of transaminase elevation is rare, monitoring should be done prior to initiation of therapy and then periodically thereafter. These agents are contraindicated in patients with type 1 DM and in patients with New York Class III or Class IV congestive heart failure. Clinically, glucose lowering is very gradual with these agents, such that individualized downward titration in insulin dosage in insulin-treated type 2 DM patients may not be needed for at least 2 weeks, and the maximum effect may not be seen for up to 12 weeks. Pioglitazone was associated with an increased bladder cancer risk consisting of four extra cases per 10,000 patients treated. A recent meta-analysis found no increased risk of bladder cancer [28], confirming the findings of the Proactive Prospective Clinical Trial in macrovascular events trial (PROactive) 10-year follow-up. Rosiglitazone prescribing was restricted in the US based on a flawed meta-analysis showing increased cardiovascular deaths. A reevaluation of the Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial failed to show increased cardiovascular risk [29]. Rosiglitazone can be prescribed only via a risk evaluation mitigation strategies (REMS) program. In regard to pioglitazone, the usual starting dose of pioglitazone is 15 mg qd, and the maximum dosage is 45 mg qd; however, in most patients, to reduce the risk of pedal edema, the maximum dose should not exceed 30 mg qd. In regard to rosiglitazone, the usual starting dose is 4 mg qd, either as a single daily dose or in divided doses. The maximum dose is 8 mg qd, but edema and heart failure risk is increased. Thiazolidinediones can enhance fertility in premenopausal women with PCOS; appropriate contraception should be used to prevent unwanted pregnancy.

α-Glucosidase Inhibition

α-Glucosidase inhibition by acarbose (Precose) and miglitol (Glyset) has a primary mode of action of decreasing postprandial blood glucoses via direct interference with the digestion and absorption of dietary carbohydrate and thus reduces postprandial glucoses. There is no hypoglycemia as monotherapy and no weight gain. Both insulin levels and lipid levels decline. These agents are most commonly used as adjunctive therapy rather than monotherapy. Both agents need to be dosed with the first bite of the meal. Increased intestinal gas formation, the most common side effect, is minimized with slow dose titration and does decrease with continued administration. They are contraindicated in type 1 DM, inflammatory bowel disease, bowel obstruction, cirrhosis, and conditions associated with maldigestion or malabsorption. In a 70 kg man, the starting dose of both acarbose and miglitol is 25 mg tid with a maximum dose of 100 mg tid.

Augmentation of Insulin Secretion

Sulfonylureas enhance insulin secretion and action. First-generation sulfonylureas should no longer be used as they have high risks of side effects, such as sustained hypoglycemia, the chlorpropamide flush

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(an Antabuse-like reaction), protein-binding interference with certain medications, and syndrome of inappropriate diuretic hormone secretion. The second- and third-generation sulfonylureas are preferred owing to their increased milligram potency, shorter duration of action, and better side-effect profile.

Prior concerns about possible cardiotoxicity of sulfonylureas related to the University Group Diabetes Program (UGDP) study have generally disappeared, given the emergence of data to support the safety of these agents from the cardiovascular prospective in the UKPDS. Glimepiride (Amaryl), a third-generation sulfonylurea, has theoretical benefits in terms of reduced risk of hypoglycemia, potentially lower risk of adverse cardiovascular effects, and perhaps reduced potential for secondary failure. Sulfonylureas are contraindicated in type 1 DM. In a 70 kg male, the usual starting dose of glimepiride is 2 mg daily with a maximum dose of 4 mg bid; the usual starting dose of glipizide ER (Glucotrol XL) is 5 mg qd with a maximum dose of 20 mg qd.

The insulin secretagogue in the glinide class, repaglinide (Prandin), is dosed prior to meals, producing an abrupt secretion of insulin secretion, designed to assist in the control of postprandial glucose levels. There is potential, although unproven, for a reduction in weight gain that is so frequently seen with sulfonylureas. Theoretical potential to reduce secondary failure rates is also a purported benefit. In a 70 kg man, the usual starting dose of 0.5 mg prior to each meal with a maximum dosage of 16 mg daily in divided doses premeal. Coadministration with gemfibrozil can result in an increase in repaglinide exposure. It is contraindicated in type 1 DM.

Nateglinide (Starlix), a phenylalanine derivative, is an insulin secretagogue, the effects of which are more glucose dependent. Nateglinide dosed prior to meals produces an abrupt spurt of insulin. However, in contrast to repaglinide, nateglinide restores early insulin secretion that is lost as β-cell function declines prior to the development of type 2 DM. Early insulin secretion is important, shutting off hepatic glucose production in preparation for the prandial glucose rise. Weight gain is attenuated, and hypoglycemia is very rare. Switching from a sulfonylurea to nateglinide can result in a slight rise in fasting plasma glucose; however, as postprandial glucose is significantly improved, the HbAlc may be maintained or lowered. This is due to the fact that postprandial glucose contributes more to the HbA1c than fasting or preprandial glucoses do when the HbA1c is <8.0 %. In a 70 kg male, the usual starting dose and maximum dose are 120 mg with each meal; in individuals with an HbA1c close to normal, the starting dose can be 60 mg tid. Use with caution in moderate to severe hepatic impairment. It is contraindicated in type 1 DM.

Dipeptidyl Peptidase IV (DPP-IV) Inhibitors

DPP-IV inhibitors inhibit the enzyme DPP-IV which degrades native glucagon-like peptide-1 (GLP-1) resulting in a return of reduced GLP-1 levels to normal and resulting in glucose-dependent insulin secretion and decreased glucagon levels. Their effects are mainly postprandial, as monotherapy does not cause hypoglycemia and is weight and lipid neutral. DPP-IV inhibitor dosing varies according to creatinine clearance (CrCl) with the exception of linagliptin (Tradjenta). In a 70 kg male, starting and maximum doses are as follows with sitagliptin (Januvia): 25 mg qd for CrCl $<$ 30 ml/min, 50 mg qd for CrCl 30–49 ml/min, and 100 mg qd for CrCl $\geq$ 50 ml/min. In 70 kg male, starting and maximum doses for saxagliptin (Onglyza) are 2.5 mg qd for CrCl $\leq$ 50 ml/min or with coadministration of a strong inhibitor of CYP3A4/5 and 5 mg qd for CrCl $>$ 50 ml/min. For linagliptin, in a 70 kg man, both starting and maximum doses are 5 mg qd due to the mainly fecal excretion of the drug, regardless of CrCL. Linagliptin should not be coadministered with medications that are strong inducers of either CYP3A4 or *P*-glycoprotein as its efficacy will be decreased. For alogliptin (Nesina), in a 70 kg man, both starting and maximum doses are 6.25 mg qd for CrCl $<$ 30 ml.min, 12.5 mg qd for CrCl 30–59 ml/min, and 25 mg qd for CrCl $\geq$ 60 ml/min. Side effects of DPP-IV inhibitors include upper respiratory infections, nasopharyngitis, headache, and urinary tract infections. Early on, an association of increased risk of pancreatitis and pancreatic cancer was noted in post-marketing reports; however, this has been negated by findings of the US Food and Drug

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Administration (FDA) and the European Medicines Agency (EMA). They are contraindicated in type 1 DM.

Bromocriptine Mesylate

Once daily bromocriptine mesylate (Cycloset), a dopamine agonist, increases the level of bromocriptine for 4–5 h. It is generally used as a second- or third-line agent. It reduces fasting glucose levels without increasing insulin levels, does not cause hypoglycemia as monotherapy, and is weight and lipid neutral. The precise mode of action is unknown. In a 70 kg man, the starting dose is 0.8 mg qam within 2 h of awakening and should be dosed with food. It can be titrated weekly to a maximum dose of 4.8 mg qd with the same dosing considerations. Side effects are the rate-limiting step and include nausea, anorexia, dyspepsia, emesis, dizziness, fatigue, and asthenia. There are multiple potential drug interactions when it is coadministered with strong inhibitors/inducers/substrates of the CYP3A4 pathway and medications that are highly protein bound. It is contraindicated in type 1 DM and in patients with syncopal migraine as it may precipitate hypotension.

Colesevelam

Colesevelam's (Welchol's) mode of action regarding glucose lowering is unknown; it is not approved as monotherapy. Fasting glucose levels are reduced without increasing insulin levels. It is weight neutral. LDL-C levels are reduced; however, triglyceride levels are increased in insulin-treated patients. In a 70 kg man, the usual starting dose is three 625 mg tablets with lunch and dinner or six 625 mg tablets at dinner. Colesevelam can cause constipation. It reduces levels of many medications such as cyclosporine, levothyroxine, oral contraceptives that include ethinyl estradiol/norethindrone, and the second- and third-generation sulfonylureas. Reports also show reduced levels of phenytoin and lower international normalized ratio (INR) levels in warfarin-treated patients. The main side effect is constipation. It is contraindicated in type 1 DM.

Sodium-Glucose Cotransporter-2 (SGLT-2) Inhibitors

Although the renal threshold for glucose in the individual without DM is 180 mg/dl, in the individual with DM, the renal threshold is closer to 240 mg/dl, thereby causing increased reabsorption of glucose. The SGLT-2 receptors transport approximately 90 % of filtered glucose from the proximal tubule in the kidney into the interstitial cells for reabsorption. SGLT-2 inhibitors reduce the glucose reabsorption and increase urinary glucose excretion by approximately 70 g/day resulting in a 280 kcal caloric purge and in improved fasting and postprandial glycemic control, weight loss, and reduced systolic blood pressure. As monotherapy, they do not cause hypoglycemia. A slight increase in LDL-C is seen. In a 70 kg man, the usual starting dose of canagliflozin (Invokana) is 100 mg qam with an estimated glomerular filtration rate (eGFR) of $\geq$45 ml/min; the dose can be titrated to 300 mg qam if eGFR is $\geq$60 ml.min. With dapagliflozin (Farxiga), the usual starting dose is 5 mg qam if eGFR is $\geq$60 ml/min and can be up-titrated to 10 mg qam if eGFR is maintained at $\geq$60 ml/min. With empagliflozin (Jardiance), the usual starting dose is 10 mg qam with a maximum dose of 25 mg qam if the eGFR is maintained at $\geq$45 ml/min. The most common side effect is genital mycotic infections in women and uncircumcised men. Urinary tract infections, thirst, constipation, hypovolemia, and a transient reduction in creatinine clearance can be seen. When initiating therapy or increasing dosage, it is prudent to review diuretic and antihypertensive therapy and reduce doses in anticipation of the blood pressure-lowering effects. Patients should be counseled on maintaining good oral fluid intake of at least 64 oz daily of non-caffeinated beverages. As monotherapy, they do not cause hypoglycemia. Hypoglycemia can occur when used concurrently with insulin or secretagogues such that down-titration of insulin and/or secretagogues is appropriate early on. They are contraindicated in type 1 DM.

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Injectable Incretin Therapy

GLP-1 receptor agonists bind to the GLP-1 receptor and raise GLP-1 levels to pharmacologic levels resulting in suppression of glucagon hypersecretion, restoration of first-phase insulin secretion, enhancement of glucose-dependent insulin secretion, delayed gastric emptying, and promotion of both the physical sensation of gastric fullness and central satiety. They are resistant to degradation by DPP-IV. When used as monotherapy, they do not cause hypoglycemia; they facilitate weight loss. They are favorable agents to use as monotherapy in metformin-contraindicated patients as they do not promote weight gain. Side effects include nausea, dyspepsia, emesis, diarrhea, and constipation. The agents with longer half-lives generally have fewer gastrointestinal side effects. They are contraindicated in patients with either a personal or family history of either medullary thyroid cancer or multiple endocrine neoplasia syndrome 2 (MEN2) due to studies demonstrating C-cell hyperplasia in mice and rats and the association of medullary thyroid cancer to C-cell hyperplasia. In primates and humans, there has been no sustained elevation in calcitonin levels. Additionally, there have been no cases of C-cell hyperplasia. If a thyroid nodule is noted on physical examination or radiologic study, the patient should be referred to an endocrinologist for evaluation (see Table 3 for specifics of individual medications). GLP-1 receptor analogs are approved only for use of type 2 DM. Post-marketing reports indicated a potential association with an increased risk of pancreatic cancer and pancreatitis, but the US FDA and the EMA have not found such a relationship in the clinical trial data.

Pramlintide (Symlin), an analog of the neuroendocrine hormone amylin, is secreted by the ß-cells in response to the intake of food. Pramlintide suppresses the hypersecretion of glucagon and results in delayed gastric emptying and decreased food intake and increased central satiety thus improving postprandial glucose levels. It is approved for use in both type 1 and type 2 DM patients. In type 1 DM patients, pramlintide should be initiated at a dose of 15 mcg sc prior to major meals with gradual titration to 30–60 mcg premeal if tolerated. In type 2 DM patients, the starting dose is 60 mcg prior to major meals with up-titration to 120 mcg as tolerated. Nausea is the rate-limiting step in dosage titration. Extreme caution must be used when using in conjunction with insulin as there is an increase in the risk of hypoglycemia. Reduction in premeal RAA by 50 % is recommended in insulin users with increased HBGM needed for both safety and efficacy.

Insulin Therapy

Insulin therapy in type 2 DM patients is indicated in situations where patients are acutely decompensated and are more insulin resistant due to intercurrent illnesses. Clearly, short-term insulin therapy can reestablish glycemic control acutely in many individuals. However, reevaluation of endogenous insulin production with C-peptide determinations is important. Most obese patients with type 2 DM have normal or fairly elevated C-peptide levels, assuming they are not glucotoxic from antecedent chronic hyperglycemia. The initiation of insulin therapy in a type 2 DM patient remains controversial in terms of indications and the optimal insulin regimen. The dilemma revolves around the obese C-peptide-positive patient who was achieving good glycemic control in the short term with insulin. This individual often suffers progressive obesity and worsening glycemic control owing to worsening insulin resistance, thereby increasing requirements for exogenous insulin. Thus, frequently insulin therapy in an obese C-peptide-positive patient fails to achieve its primary goal of sustained improved glycemic control. Additionally, perpetuation of the obese state, or indeed worsening thereof, in conjunction with progressive hyperinsulinemia raises concerns about the impact of this worsened metabolic milieu on hypertension, dyslipidemia, and the atherosclerotic process. Initiation of insulin therapy should therefore be undertaken cautiously in most patients and progress carefully monitored in terms not only of glycemic control but also of hypertension, dyslipidemia, and obesity.

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Table 3 Glucagon-like peptide-1 analogs

	Exenatide (Byetta)	Liraglutide (Victoza)	Exenatide LAR (Bydureon)	Albiglutide (Tanzeum)	Dulaglutide (Trulicity)
Homology to native GLP-1	50 %	97 %	50 %	79 %	90 %
t½	2.5 h	13 h	5 days	>3 days	5 days
Dose frequency	bid	qd	qwk	qwk	qwk
Starting dose	5 mcg sc bid	0.6 mg sc qd	2 mg sc q wk	30 mg sc qwk	0.75 mg sc qwk
Maximum dose	10 mcg sc bid	Weekly titration in 0.6 mg qd increments to max dose of 1.8 mg sq qd	2 mg sc qwk	50 mg sc qwk	1.5 mg sc qwk
Packaging	Multidose pen with fixed dosing	Multidose pen with flexible dosing	Reconstitution vial/syringe	Reconstitution single-dose pen	Single-dose pen with prefilled solution
			Reconstitution single-dose pen		
Dose adjustment for renal disease	Yes	No	Yes	No	No
					No data with CrCl < 30 ml/min

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Many insulin regimens have been used to treat type 2 DM, most being similar to those used in the type 1 DM setting. Trends have focused on the use of bedtime basal insulin therapy in these individuals on the grounds that it can maximally affect the dawn hepatic glucose output/disposal and peak insulin resistance, thereby achieving the best possible fasting blood glucose and minimizing glucotoxicity. Minimizing glucotoxicity facilitates daytime β-cell secretory function and minimizes the need for daytime insulin therapy. Combination therapy with insulin-sensitizing agents and insulin is theoretically sound, reducing the need for exogenous insulin. One such regimen has been the use of a bedtime dose of basal insulin such as insulin glargine insulin glargine U-300, or insulin detemir at a dose of 0.2 units/kg of body weight coupled with daytime oral agents/GLP-1 receptor agonists. An alternative dosing is to use insulin glargine insulin glargine U-300 or insulin detemir starting at a dose of 10 units and titrating accordingly. Several titration regimens have been demonstrated to be both safe and successful [30]. Although hypoglycemia is relatively uncommon in type 2 DM patients owing to their fundamental insulin resistance, it can occur in those on insulin or sulfonylureas. Sulfonylureas should be used with caution in combination with insulin, especially in patients with hepatic or renal impairment and in the elderly. The Outcomes Reduction with Initial Glargine Intervention (ORIGIN) trial with insulin glargine showed a neutral effect on cardiovascular events and cancer risk in patients with cardiovascular risk factors plus impaired fasting glucose, impaired glucose tolerance, or overt type 2 DM [31].

Weight-Based Approaches

Pharmacotherapy for obesity is an ever-changing environment with available medications as an adjunct to diet and exercise. Approved oral medications include phentermine/topiramate extended-release (Qsymia), lorcaserin (Belviq), and naltrexone HCL/bupropion HCL (Contrave). The injectable GLP-1 analog liraglutide has been approved at higher doses than that approved for treatment of type 2 DM (Saxenda). The rate-limiting step for most individuals is cost with health insurance plans frequently carving out pharmacotherapy coverage for obesity. Bariatric surgery, despite claims, is a treatment, not a cure, for type 2 DM. Careful medical nutrition therapy and exercise is important. Recidivism rates remain high in bariatric surgery patients.

Prevention of type 2 DM

Can type 2 DM be prevented? The Diabetes Prevention Program in type 2 DM showed a 58 % risk reduction in the development of type 2 DM in patients treated with diet and exercise versus a 31 % risk reduction in patients treated with metformin. A Finnish lifestyle modification study demonstrated a similar 58 % risk reduction in developing type 2 DM in patients with impaired glucose tolerance who were randomized to a program of intensive diet and exercise. There is also data suggesting thiazolidinediones may prevent type 2 DM.

Diabetic Ketoacidosis

Diabetic ketoacidosis (DKA) is the ultimate expression of absolute insulin deficiency resulting in uncontrolled lipolysis, increased free fatty acid delivery to the liver, and ultimately accelerated ketone body production. Insulin deficiency at the level of the liver results in uncontrolled hepatic glucose output via gluconeogenesis and glycogenolysis. With insulin-mediated skeletal muscle glucose uptake being inhibited, hyperglycemia rapidly ensues. The attendant osmotic diuresis due to hyperglycemia results in progressive dehydration and a decreasing glomerular filtration rate. Dehydration may be compounded by

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gastrointestinal fluid losses (e.g., emesis from ketones or a primary gastrointestinal illness with concurrent diarrhea). Insensible fluid losses from febrile illness may further compound the dehydration.

Diagnosis of DKA is fairly characteristic in the newly presenting or established type 1 DM patient. The history of polydipsia, polyuria, weight loss, and Kussmaul's respirations is virtually pathognomonic. Physical examination is directed at assessing the level of hydration (e.g., orthostasis) and the underlying precipitating illness. Measurement of serum ketones, urine ketones, and blood glucose levels can rapidly confirm the clinical suspicion, with arterial pH, serum bicarbonate, and ketones validating the diagnosis. A thorough search for an underlying precipitating illness remains axiomatic (e.g., urosepsis, respiratory tract infection, or silent myocardial infarction). Treatment is directed at correcting (1) dehydration/hypotension, (2) ketonemia/acidosis, (3) uncontrolled hepatic glucose output/hyperglycemia, and (4) insulin resistance of the DKA/underlying illness. Of course, specific treatment is directed to any defined underlying illnesses.

Dehydration and hypotension require urgent treatment with a 5- to 6-L deficit to be anticipated in most individuals. Initial treatment is 0.9 % NaCl, with 1–2 L/h being given for the first 2 h and flow rates thereafter being titrated to the individual's clinical status. Potassium replacement at a concentration of 10–40 mEq/L is critical to replace the usual deficits of more than 5 mEq/kg once the patient's initial serum potassium level is known and urine output is documented. Giving 50 % of the potassium as KC1 and 50 % as KPO_4 appears theoretically sound, but routine phosphate replacement has not been shown to alter the clinical outcome. Bicarbonate therapy is generally reserved for patients with a pH of less than 7.0, plasma bicarbonate less than 5.0 mEq/L, severe hyperkalemia, or a deep coma. Bicarbonate is administered by slow infusion 50–100 mEq over 1–2 h with the therapeutic end point being a pH higher than 7.1 rather than normalization of the pH. Overzealous use of bicarbonate can result in severe hypokalemia with attendant risk of arrhythmias, paradoxical central nervous system acidosis, and possible lactic acidosis due to tissue hypoxia. Intravenous insulin therapy is initiated at a dose of 0.1 U/kg/h with rapid titration every hour should a 75–100 mg/dl/h decrease in blood glucose not be achieved. Insulin therapy at this relatively high dose is needed to combat the insulin resistance of the hormonal milieu of DKA (i.e., high levels of glucagon, cortisol, growth hormone, and catecholamines). Given that hepatic glucose output is more rapidly controlled than ketogenesis, the insulin infusion rate can be maintained by switching the intravenous infusion to dextrose 5–10 % when the blood glucose is less than 250 mg/dl. The insulin infusion is continued until the patient is ketone-free, clinically well, and able to resume oral feeding. It is of paramount importance that subcutaneous insulin be instituted promptly at the time of refeeding.

Flow sheets should be generated documenting the following:

1. Patient admission weight relative to previous weights with serial weights every 6–12 h, urine ketones, and fluid balance
2. Vital signs and mental status every 1–2 h
3. Bedside glucose monitoring every 1–2 h
4. Urine ketones every 1–2 h
5. Fluid balance
6. Blood gases and arterial pH on admission, repeating until pH is over 7.1
7. Serum potassium on admission and then every 2–4 h
8. Serum ketones on admission and then every 2–4 h
9. Complete blood count, serum chemistries, chest roentgenogram, electrocardiogram, and appropriate cultures on admission
10. Abnormal chemistries other than potassium repeated every 4 h until normal

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Family Medicine
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Thyroid Disease

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Thyroid diseases are common endocrine disorders that may seriously affect patients' health and often require lifelong treatment and monitoring. This chapter reviews the most common thyroid problems, with emphasis on clinical presentation, diagnosis, treatment, and follow-up.

Screening for Thyroid Disease

The American Academy of Family Physicians, American College of Physicians, US Preventive Services Task Force, and the Royal College of Physicians all concluded there is not enough evidence to recommend screening in the general population. However, the American Thyroid Association recommends measuring a thyroid-stimulating hormone (TSH) level in all patients at age 35 and every 5 years thereafter, even though they note a serious lack of efficacy data, especially in men and younger women [1]. Laboratory measurement of thyroid function is recommended in certain patient groups who are at higher risk for thyroid disease. The American Association of Clinical Endocrinologists recommends TSH measurement in women of childbearing age before pregnancy or during the first trimester [2]. Patients with atrial fibrillation or hyperlipidemia should have their TSH measured at least once. Annual laboratory measurement of thyroid function is recommended for patients with diabetes or Down syndrome. Patients taking certain medications such as amiodarone and lithium require periodic TSH measurement as these medications may alter thyroid function.

Hyperthyroidism

Thyrotoxicosis is caused by excess thyroid hormone. The prevalence of hyperthyroidism in community-based studies has been estimated at 2 % for women and 0.2 % for men [3]. As many as 15 % of cases of hyperthyroidism occur in patients older than 60 years, of which a large percentage was taking thyroid home preparation [4]. Excluding excess thyroid hormone ingestion, approximately 90 % of hyperthyroidism is caused by Graves' disease. Thyrotoxic nodules and thyroiditis account for almost all other cases [5]. Women are more commonly affected by hyperthyroidism than men, with reported ratios varying from 4:1 to 10:1 [5, 6].

Health Risks

Hyperthyroidism causes or exacerbates several other health problems, with cardiovascular complications being most important. Atrial fibrillation is the most common complication, occurring in 8–22 % of

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thyrotoxic patients, and these patients are at increased risk of stroke from atrial thromboembolism [7]. Cardiac failure, angina, myocardial infarction, and sudden death have been associated with thyrotoxicosis [8]. Thyroid storm causes multisystem involvement and carries a high risk of mortality (10–75 %) [5]. Calcium and bone metabolism are affected by thyrotoxicosis, leading to osteoporosis and an increased risk of bone fracture. Atrial fibrillation and osteoporosis may occur with even subclinical hyperthyroidism [9]. Certain ethnic groups may suffer less common complications. Periodic paralysis may occur as a result of thyrotoxicosis and is observed mostly in Oriental populations [10].

Family Impact

As with any chronic disease, hyperthyroidism may place stress on the family system. The affected family member may experience emotional labiality, heat intolerance, and fatigue, all of which strain relationships within the family. Hyperthyroidism may be especially stressful prior to diagnosis as the patient and family may not attribute their symptoms to a physiologic illness versus psychological. Symptoms of hyperthyroidism may adversely affect job performance and subsequently produce additional stress and loss of income.

Clinical Presentation

Symptoms of thyrotoxicosis, arranged in order of frequency, are listed in Table 1, and the chief complaint can be any one of these symptoms. A directed history usually reveals up to eight symptoms, although some patients, especially in the geriatric age group, may report only a few [5, 11].

Patients often report weight loss, even with a history of increased appetite. Heat intolerance is usually described as preferring room temperatures cooler than do other family members or preferring winter to summer. Fatigue and weakness of proximal muscles can be reported as difficulty climbing stairs.

It is of note that abdominal symptoms of vomiting, nausea, and abdominal pain, although previously thought to be rare or present only preceding thyroid storm, may be relatively common [11]. Patients who present with these abdominal symptoms as their chief complaint may be at higher risk of missed diagnosis. Vomiting can occur without nausea and tends to be postprandial. Abdominal pain is usually epigastric or left upper quadrant in location, unrelated to meals, and described as sharp or cramping [11].

Physical findings of thyrotoxicosis are listed in Table 1, and five or more are typically present. Goiter is the most frequent sign, but the enlargement may be only mild or difficult to appreciate, especially when it occupies a substernal location. The skin tends to be warm, moist, and velvety smooth. A fine tremor of outstretched hands is usually present, and deep tendon reflexes are often brisk with a rapid relaxation phase. Lid lag may be present with any cause of thyrotoxicosis; exophthalmos is specific to Graves' disease. Onycholysis may be present, typically of the ring fingers, causing separation of the nail from the distal nail bed and difficulty cleaning the nails (Plummer's nails) [5, 10, 16].

Laboratory Evaluation

Confirmation of clinical thyrotoxicosis is accomplished by measuring thyrotropin (TSH) by a highly sensitive assay and is further substantiated with measurement or estimate of free thyroxine (T_4) and sometimes free triiodothyronine (T_3). These hormones are clinically active only when they are not protein bound. A diagnostic approach to the patient with thyrotoxicosis is shown in Fig. 1. Along with the TSH,

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Table 1 Signs and symptoms of thyrotoxicosis (in order of frequency)

Symptoms/signs	Percent of patients
Symptoms	
Nervousness	88
Weight loss	83
Heat intolerance	75
Dyspnea	70
Palpitation	69
Increased sweating	62
Fatigue	58
Tachycardia	51
Eye complaints	49
Weakness	47
Increased appetite	45
Vomiting	44
Swelling of legs	38
Chest pain	36
History of fever	36
Nausea	28
Diarrhea	26
Frequent bowel movements	21
Abdominal pain	20
Swelling in neck	16
Anorexia	13
Constipation	12
Dysphagia	12
Hair loss	4
Signs	
Goiter	96
Skin changes (smooth, moist)	85
Tremor	79
Tachycardia (>100 bpm)	76
Systolic murmur	76
Ocular signs (e.g., lid lag)	60
Brisk deep tendon reflexes	56
Pulse pressure ≥70 mmHg	52
Bruit over thyroid	47
Atrial fibrillation	8
Gynecomastia	7
Splenomegaly	7

Source: See ref. [11]

initial tests are usually free T_4 and free T_3. Although the reliability of some methods has been questioned in the past, newer assays of free T_4 and free T_3 are more dependable [5, 12]. Euthyroid patients may have an elevated total T_4 due to excess thyroid-binding proteins, such as found in pregnancy, use of estrogens, or some inherited disorders.

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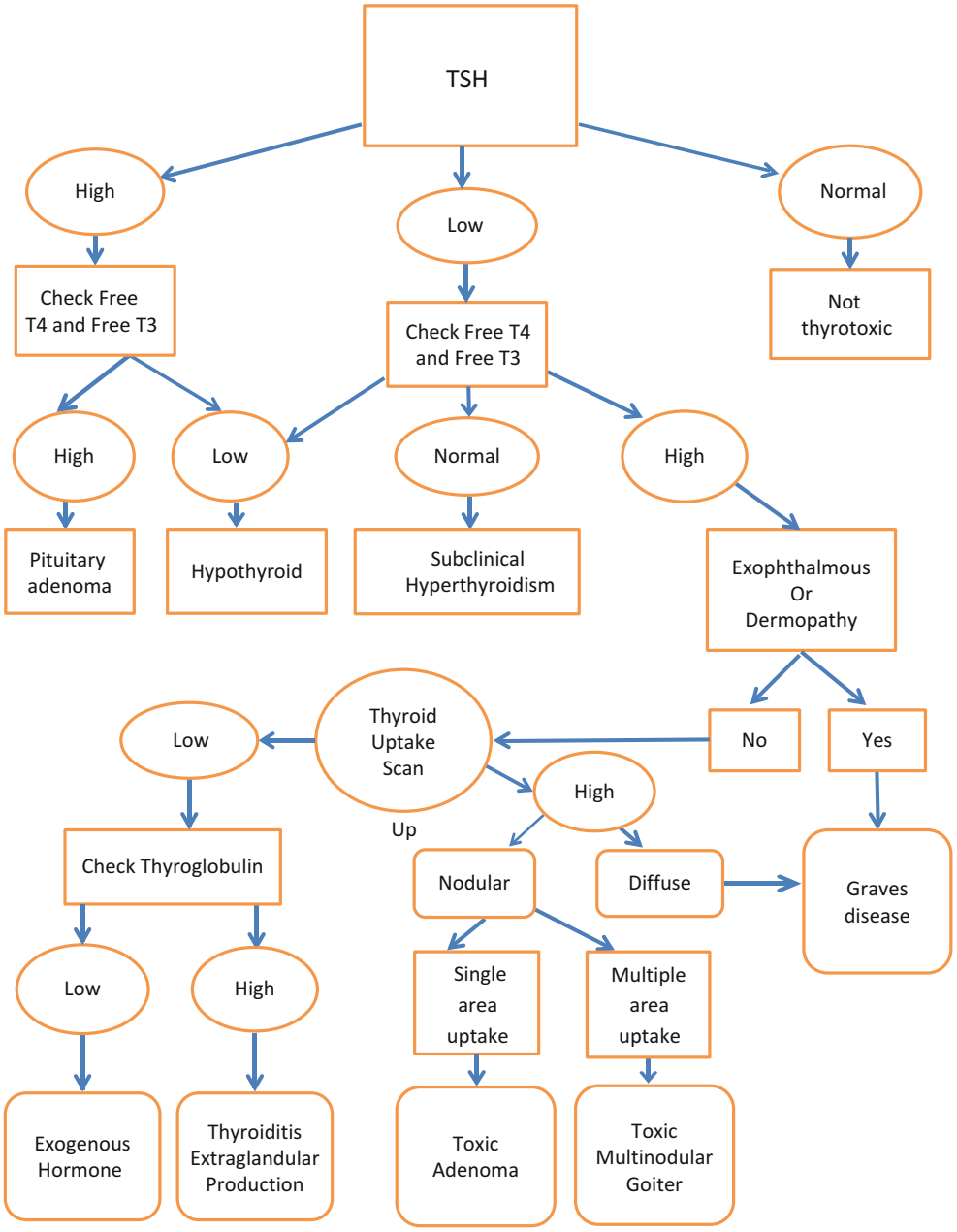

Fig. 1 Diagnostic approach to the patient with thyrotoxicosis (see attached document)

Through pituitary feedback mechanisms, TSH levels inversely follow free T_4 levels. Measurement of TSH by a highly sensitive assay in patients with hyperthyroidism yields a value far below the normal range and helps confirm the diagnosis. The sensitive TSH is especially useful in patients with concomitant illnesses or on medications that can alter T_4 [12]. Because TSH is a more sensitive measure of thyroid status, patients may have an abnormally low TSH with a normal free T_4. They are considered to have subclinical hyperthyroidism [5, 9]. TSH can also be moderately low as a result of nonthyroidal illness or medications (glucocorticoids and dopamine) and is occasionally low in healthy people, particularly the elderly [13]. The TSH level in these settings is usually not less than 0.1 μU/mL. When the TSH level is less than the lower limit of a sensitive assay (undetectable), thyrotoxicosis is usually present [5]. Rarely, a TSH-secreting adenoma causes hyperthyroidism with an elevated TSH.

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When TSH is low but free T_4 is normal, measurement of free T_3 should be obtained and, if elevated, confirms clinical thyrotoxicosis. This condition, known as T_3 toxicosis, occurs occasionally in patients with early Graves' disease or a thyrotoxic nodule [5, 10].

Nuclear medicine scans of the thyroid are useful for assessing thyroid size to determine if thyroid nodules are functioning (hot) or nonfunctioning (cold) and to measure the level of thyroid function (thyroid uptake). Of the radionuclides available for thyroid scans, iodine 123 (^{123}I) is optimal. Technetium may also be used for thyroid imaging, but measurement of function is less reliable, as a nonfunctioning nodule by the ^{123}I scan may demonstrate function with technetium [5].

Graves' Disease

The disease described by Robert Graves in 1835 is the most common cause of hyperthyroidism [5]. It is caused by an autoimmune process, closely related to chronic lymphocytic (Hashimoto's) thyroiditis. The onset of Graves' disease may follow some physical or psychological stress, and a family history of thyroid disease is often present [5, 10].

Signs and Symptoms

All the clinical manifestations of thyrotoxicosis may be present in Graves' disease, with additional specific findings of ophthalmopathy and dermopathy. A diffuse goiter occurs in most patients and may cause neck swelling or dysphagia. On palpation, the thyroid is nontender and somewhat soft. Eye problems occur in more than 50 % of patients and include pressure sensation, irritation, gritty feeling, lacrimation, a change in appearance, and occasional blurred vision or diplopia. The exophthalmos occasionally causes marked eye irritation or even blindness. Dermopathy occurs in 1–2 % of patients and causes raised, firm, nontender, intradermal nodules on the anterior surfaces of the lower legs. Clubbing of the nails (acropachy) is a rare manifestation of Graves' disease [5, 10].

Diagnosis

Graves' disease is diagnosed by confirming hyperthyroidism with thyroid function tests (free T_4), along with one or more physical findings specific to the disease. If a goiter is present without exophthalmos or dermopathy, Graves' disease may be difficult to distinguish from subacute painless thyroiditis or postpartum thyroiditis. A reliable history of chronic hyperthyroid symptoms strongly suggests Graves' disease, and an elevated thyroid uptake confirms this diagnosis when it remains in doubt [5, 10]. Thyrotropin receptor (TSH-R) antibodies are present in most patients with Graves' disease, but they are of limited diagnostic value. High titers of these antibodies may identify those patients who are unlikely to go into remission. Measurement of TSH-R antibodies in pregnant patients with thyrotoxicosis may be useful [5].

Treatment

Therapy of Graves' disease is directed toward controlling the effects of excess thyroid hormone and reducing the production of additional hormone [13]. Beta-blockers are especially effective in controlling the tachycardia, tremor, and other symptoms related to excess hormone. Atenolol is often preferred because it has the advantages of single daily dosing and beta-1 selectivity. Alternatively, propranolol is begun at 20–40 mg 2–4 times daily and increased every few days until the heart rate is within the normal range [10]. When beta-blockers are contraindicated, diltiazem or clonidine may be effective [14, 15]. Controlling hormone production may be accomplished with antithyroid medications, radioiodine ablation, or

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surgery. Choice of treatment is influenced by the clinical presentation, the age of the patient, and the patient's ability and willingness to comply with a treatment regimen [5, 10].

Antithyroid medications available in the United States to control thyroid hormone production are the thionamides, methimazole, or propylthiouracil. In addition to blocking production of thyroid hormone, these medications may alter the course of the disease via their immunosuppressive effects [16]. Reported remission rates vary widely and are probably higher in patients with less severe hyperthyroidism, short duration of illness, and small goiter. The duration of treatment is usually 6 months to 2 years. The remission rate can be as high as 60 % if treatment is continued for 2 years. Failure to achieve remission after 2 years of treatment is an indication for alternate therapy [5, 10, 16].

Initial adult dosage of methimazole is 20–30 mg/day divided into two doses. In patients with severe hyperthyroidism and a large goiter, the higher dose is warranted. Euthyroid status, determined clinically and with thyroid function tests (T_4 and T_3), is usually achieved within 4–6 weeks, and the dosage is reduced incrementally every 4–6 weeks to a maintenance dose of 2.5–10 mg/day given in a single dose. TSH is not useful for following the response to treatment, as it may remain suppressed for months after T_4 and T_3 normalize. The initial dose of propylthiouracil is usually 300 mg/day, and maintenance is 50–100 mg/day. Both must be divided into three doses [5, 10]. Either of these drugs may cause rash, leukopenia, and (rarely) agranulocytosis. Patients should be cautioned about these side effects. Methimazole has the advantages of lower risk of agranulocytosis, a longer half-life allowing usage on a once-a-day schedule, and more rapid return to euthyroid status. Propylthiouracil is preferable during pregnancy, lactation, or thyroid storm [5, 10]. Patients with mild hyperthyroidism and small goiters or those with goiters that shrink during antithyroid medication therapy may go into remission with a prolonged course of antithyroid medications.

Iodine 131 ablation may be used for definitive treatment for patients with more severe hyperthyroidism and large goiters to permanently destroy thyroid tissue sufficiently to reduce hormone production to normal levels. This option has the advantage of low cost and low complication rate. This treatment may be used initially in patients with mild thyrotoxicosis. Patients who are elderly or have severe thyrotoxicosis should first be treated with antithyroid medications because ^{131}I ablation can induce a temporary exacerbation of thyrotoxicosis or thyroid storm [10]. The amount of radiation used can be calculated based on the patient's weight, gland size, and thyroid uptake. A major disadvantage of this treatment is the high prevalence of hypothyroidism (>90 %), which continues to increase with the passage of time [5]. Therefore, a patient's ability to comply with lifelong replacement therapy should be considered when choosing this treatment. Pregnancy is a contraindication to ^{131}I.

Subtotal thyroidectomy is an alternate method of permanently controlling thyroid hormone production. This treatment is indicated when the goiter is large, particularly if obstructive symptoms are present. Surgery is also indicated in children who fail a trial of antithyroid medication. The disadvantages of surgery include the cost and risk of surgical complications. Following surgery for Graves' disease, hypothyroidism has been reported in 53 % of patients and recurrence of hyperthyroidism in 3.4 % [10].

Follow-Up

Regardless of the treatment used, Graves' disease requires lifelong monitoring. Patients treated with antithyroid medications who go into remission must be followed for possible relapses and are at a small risk of late hypothyroidism. After treatment with ^{131}I ablation or surgery, patients require chronic periodic monitoring for development of hypothyroidism. Once hypothyroidism occurs, lifelong hormone replacement is necessary [5, 10].

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Thyrotoxic Nodule

An autonomously functioning thyroid nodule may cause thyrotoxicosis with typical hyperthyroid symptoms. Physical examination reveals a thyroid nodule, and findings specific to Graves' disease are absent. The diagnosis is confirmed with an elevated free T_4, low TSH, and a hot nodule on radioiodine scan. Fine-needle aspiration is indicated if the nodule is not hot on nuclear medicine scan, as with other nontoxic nodules.

Treatment is with ^{131}I ablation or occasionally surgery. Antithyroid medications may be used but are not typically prescribed for thyrotoxic nodules. Hypothyroidism following ^{131}I ablation is less common than with Graves' disease, although a 40 % long-term prevalence of hypothyroidism has been reported [17]. Indications for surgery include a thyrotoxic nodule that is very large or progressively enlarging or other signs suggestive of thyroid cancer [5].

The nodule may persist after ablation treatment, and ongoing monitoring by physical examination is needed to identify any increase in size. Should the nodule or adjacent tissue enlarge, further evaluation for possible thyroid cancer is required. Periodic monitoring for possible hypothyroidism also is necessary.

Thyroiditis

Thyroiditis is defined as an inflammatory process involving the thyroid gland. This inflammation may cause thyrotoxicosis due to unregulated release of thyroid hormone from an injured gland. There are several types of thyroiditis, each with a different clinical picture; three are discussed below. Hashimoto's thyroiditis is discussed in the next section, and postpartum thyroiditis is discussed in the section on pregnancy. Measurement of ^{123}I thyroid uptake is useful in any patient with thyrotoxicosis and suspected thyroiditis. Elevated free T_4 with diminished thyroid uptake confirms thyrotoxicosis due to thyroiditis.

Subacute painful (granulomatous) thyroiditis is probably caused by a viral infection and is the type of thyroiditis that most commonly results in thyrotoxicosis. Patients present with an exquisitely tender, firm, asymmetric nodular thyroid gland. They have symptoms of neck pain, a flu-like syndrome, and symptoms of thyrotoxicosis. The erythrocyte sedimentation rate is elevated, and antithyroid antibodies are absent. These patients usually go through four phases: (1) hyperthyroidism lasting 3–6 weeks, (2) euthyroid status for a few weeks, (3) hypothyroidism lasting weeks to months, and (4) euthyroid state again. The clinical diagnosis is usually made during the hyperthyroid phase and is confirmed with an elevated free T4 and decreased uptake on ^{123}I scans. Treatment of inflammation is accomplished with aspirin, other nonsteroidal anti-inflammatory agents, or corticosteroids (prednisone 20 mg twice daily for 1 week then tapered over 2–4 weeks). Patients may require β-blocker therapy to control symptoms and tachycardia initially, but there are usually no long-term sequelae requiring treatment or monitoring [5, 18].

Subacute painless (lymphocytic) thyroiditis is an autoimmune process that may cause thyrotoxicosis. Physical examination usually reveals a mildly enlarged thyroid gland that is somewhat firm and nontender, although nearly 50 % of patients have no goiter. Antibodies to thyroid peroxidase are present in about 50 % of patients. These patients may go through the same four phases as subacute painful thyroiditis, but the euthyroid phase preceding hypothyroidism may be brief or absent. Some patients do not return to euthyroid status after hypothyroidism occurs and require chronic thyroid hormone replacement [5, 18].

Acute thyroiditis, caused by a bacterial infection, is a rare condition in developed countries because of the availability of antibiotic therapy. Patients present with acute thyrotoxicosis, fever, and a tender, enlarged thyroid gland. Treatment is directed toward controlling effects of excess thyroid hormone with

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beta-blockers and treating the infection with broad-spectrum antibiotics. Needle aspiration for culture is indicated, and abscess drainage may be necessary [5, 18].

Subclinical Hyperthyroidism

Subclinical hyperthyroidism is defined by low or undetectable serum thyroid-stimulating hormone (TSH) levels, with normal levels of free T4 and free T3. Subclinical hyperthyroidism can be divided into two categories: low but detectable TSH levels (0.1–0.4 mIU per L) and suppressed TSH levels (less than 0.1 mIU per L) [19]. Subclinical hyperthyroidism may be exogenous as a result of intentional administration of thyroid hormone to suppress thyroid malignancy or unintentional excessive hormone therapy in patients with hypothyroidism. It may also result from endogenous overproduction of thyroid hormone such as from Graves' disease, autonomous functioning thyroid adenoma, toxic multinodular goiter, and subacute/painless/postpartum thyroiditis. Subclinical hyperthyroidism should be differentiated from other causes of low TSH levels that are not related to relative thyroid overactivity, such as the use of certain drugs (dopamine and glucocorticoids), nonthyroidal illness (euthyroid sick syndrome), pituitary causes (TSH deficiency), hypothalamic causes (thyrotropin-releasing hormone deficiency), and psychiatric conditions, especially affective disorders [20].

Most patients with subclinical hyperthyroidism will not progress to overt hyperthyroidism. Cardiovascular effects of subclinical hyperthyroidism include an increase in average heart rate, increased risk of atrial arrhythmias, increased left ventricular mass, and reduced heart rate variability [20–22]. Subclinical hyperthyroidism may reduce bone mineral density (BMD), particularly in cortical bone. Patients with subclinical hyperthyroidism may experience increased signs and symptoms of adrenergic overactivity, particularly those younger than 50 years [20]. Possible associations between subclinical hyperthyroidism and quality of life parameters, cognition, and increased mortality rates are controversial [20]. The effectiveness of treatment in preventing these conditions is unknown. There is no consensus regarding screening for subclinical hyperthyroidism in the general population.

Hypothyroidism

Hypothyroidism, a deficiency of thyroid hormone, can be caused by several conditions that result in the same clinical picture. The most common causes of hypothyroidism are autoimmune thyroid diseases, including Hashimoto's thyroiditis, and previous treatment for Graves' disease. Other causes of thyroiditis, congenital hypothyroidism, and central (secondary) hypothyroidism are uncommon.

Approximately 1–2 % of the general population has spontaneous hypothyroidism: 1.9 % of the female population and 0.1 % of the male population [6]. Hypothyroidism is more common with advancing age, affecting 6.9–7.3 % of patients aged 55 or over [23, 6]. Women are affected 10 times more frequently than men. Congenital hypothyroidism occurs in 1/3,000 to 1/4,000 live births in the United States [24].

The US Preventive Services Task Force and the American Academy of Family Physicians do not recommend routine screening for hypothyroidism in asymptomatic adults [25].

Health Risks

Severe hypothyroidism may lead to coma and death if untreated. Hypothyroidism can cause bradycardia, hearing impairment, carpal tunnel syndrome, and hypercholesterolemia with increased risk of

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atherosclerotic heart disease. Dementia, depression, and suicide can be sequelae of hypothyroidism. Hashimoto's thyroiditis may be associated with primary thyroid lymphoma [19]. Elderly patients are at increased risk because concomitant illnesses are common and because the symptoms of hypothyroidism may remain unrecognized [23].

Family Issues

The depression associated with hypothyroidism may have a devastating effect on the family. Withdrawal, vegetative disturbances, apathy, and loss of motivation can affect the entire family unit. This situation is especially a problem when the diagnosis is delayed.

Clinical Presentation

The most common symptoms of hypothyroidism are cold intolerance and fatigue [25]. Other symptoms include generalized weakness, fatigue, memory loss or slowed thinking, intolerance to cold, dry skin, hair loss, hoarseness, dyspnea, anorexia, deafness, chest pain, arthralgia, and facial or peripheral edema. A modest weight gain of approximately 10 pounds is typical, but patients may actually lose weight early in the disease process due to anorexia [1]. Constipation is a common complaint. Depression is often the presenting symptom, and hypothyroidism must be considered during any depression work-up [26, 27] (see chapter ► Anxiety Disorders). Women may have heavy, prolonged menstrual periods that can lead to severe anemia [5].

Periorbital edema, peripheral edema, and pale, thick, dry skin are often the first physical signs noted. Hyperkeratosis of the knees and elbows is also common. Diastolic hypertension may be present. Delayed relaxation phase of deep tendon reflexes is common but may be subtle. When hypothyroidism is severe, mucopolysaccharides deposit in subcutaneous tissue, causing the nonpitting edema known as myxedema. Pleural and pericardial effusions, cardiomegaly, bradycardia, and prolonged QT interval are possible cardiac manifestations [5].

Laboratory Evaluation

Primary hypothyroidism is diagnosed by finding an elevated TSH and a low free T_4 [25] (Fig. 2). Patients may have other lab abnormalities including elevated C-reactive protein, hyperprolactinemia, hyponatremia, increased creatinine kinase, increased serum lipids, proteinuria, and normocytic anemia [25]. Secondary hypothyroidism is characterized by a normal or low serum TSH and a low serum T4 (Fig. 2).

Treatment

Oral synthetic L-thyroxine is the treatment of choice for hypothyroidism [12] [19, 25, 28]. The usual starting dosage is approximately 75 μg/day, but patients older than 50 years and patients with heart disease are started at a much lower dose (25 μg/day). The patient should be instructed to take the medication on an empty stomach (1 h) and should not be taken with other medications such as bile acid resins, proton pump inhibitors, calcium carbonate, and ferrous sulfate [25]. The TSH is measured every 6 weeks, and the

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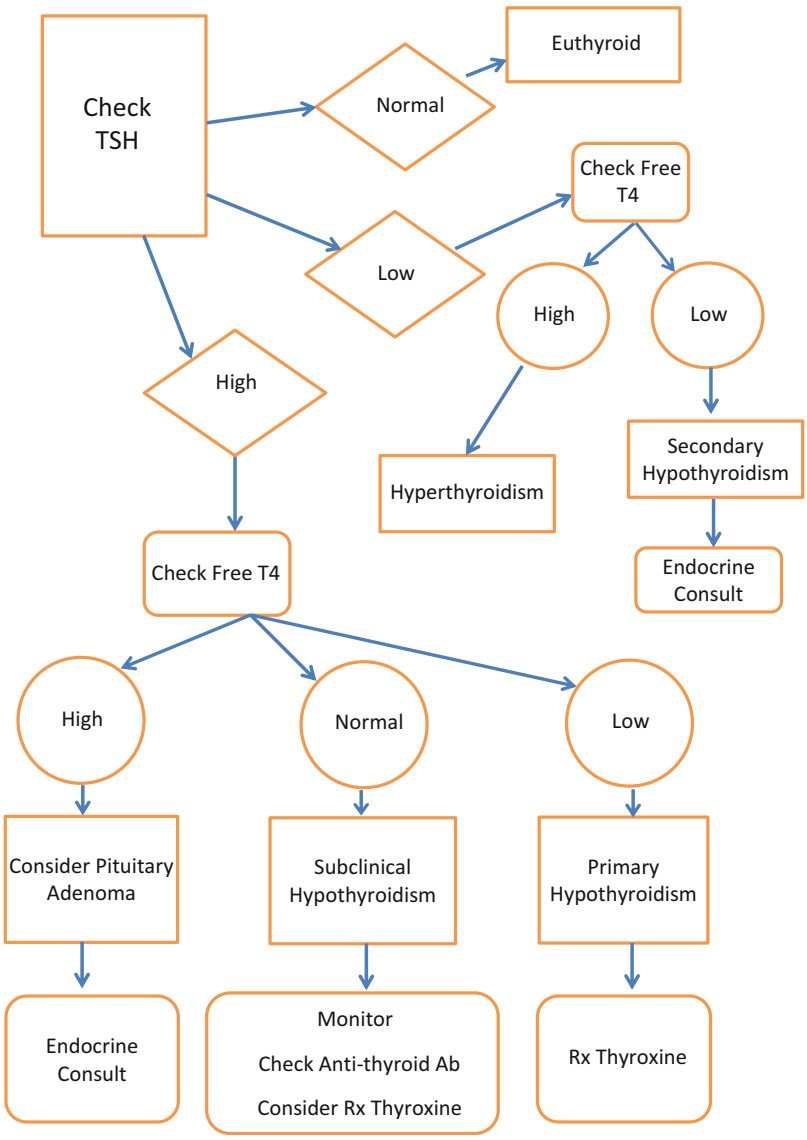

Fig. 2 Evaluation for hypothyroidism [11]

dosage of thyroxin is adjusted upward by 25 μg/day until the TSH is within the normal range, indicating the patient has returned to a euthyroid state. The target dose for most patients is approximately 1.6–1.7 μg/kg/day. Most forms of hypothyroidism are lifelong problems, and continued replacement is necessary. Once the patient is on a stable dose, the TSH level should be assayed annually to monitor appropriateness of replacement therapy [12]. Overreplacement with T4 can cause hyperthyroidism and its complications. Noncompliance with levothyroxine therapy is the most common cause of difficulty in obtaining and maintaining a patient's TSH in the therapeutic range [25].

The majority of evidence does not demonstrate a benefit of combination T4 and T3 therapy [28]. Temporary treatment with T3 may be appropriate in some patients; however, further studies are needed before that can be recommended.

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Subclinical Hypothyroidism

Subclinical hypothyroidism is defined as the presence of a high TSH with a free T_4 in the normal range. Some authors feel these patients are functionally hypothyroid relative to their own bodily requirements [12, 28] [29]. There is still some debate about whether to treat subclinical hypothyroidism. Patients often feel better with therapy, and treatment is usually indicated, especially if antithyroid antibodies are present [3]. Asymptomatic patients who have mild TSH elevation (<10 μU/mL), negative antithyroid antibodies, and no goiter may be followed without replacement [5, 19]. Since subclinical hypothyroidism may be associated with reversible hypercholesterolemia, depression, and atherosclerosis, treatment is warranted for patients with these conditions as well as infertility or pregnancy [25, 26, 30, 31].

Hashimoto's Thyroiditis

Hashimoto's thyroiditis was first described in 1912 in four patients with lymphocyte infiltration, fibrosis, and follicular cell degeneration. It causes most cases of adult-onset hypothyroidism in iodine-sufficient areas of the world [6, 18]. The etiology of the disease is autoimmune, with high serum concentrations of antibodies to thyroid peroxidase and thyroglobulin usually present [18, 29]. Like most autoimmune diseases, there is a genetic predisposition. It is most common in women (8:1) and is usually diagnosed between the ages of 30 and 50. Its incidence is increasing in developing countries [18].

Signs and Symptoms

Patients usually present with a painless, diffuse, firm goiter. Patients may complain of tenderness or fullness of the anterior neck. Dysphagia and hoarseness are occasionally present. Although hyperthyroidism is found in up to 5 % of patients during the acute stages of the disease, hypothyroidism with its various signs and symptoms is more common [19]. The presence of pain suggests the development of a primary B-cell lymphoma, a cancer associated with chronic autoimmune thyroiditis [5].

Diagnosis

The diagnosis is suspected in patients with a characteristic goiter and is confirmed in 90 % of cases by finding antibodies to thyroid peroxidase. Antithyroglobulin antibodies are also present in up to 70 % of patients, but they are rarely present alone. Therefore, this latter assay is not usually necessary for diagnosis [29]. Free T_4 and the TSH level should be obtained to determine thyroid function [18, 29]. If the goiter is very large, lobulated, or painful, fine-needle aspiration or biopsy may be indicated [5].

Treatment

Treatment of hypothyroidism is described above and requires lifelong replacement. Thyrotoxicosis usually does not occur with this type of thyroiditis, and if present is of short duration requiring only symptomatic treatment. Graves' disease may precede or follow this illness and require additional treatment.

Congenital Hypothyroidism

Thyroid dysgenesis is the cause of congenital hypothyroidism in 80 % of patients, and various problems with thyroid hormone production and regulation account for the rest. Severe growth and mental retardation (cretinism) can occur, but these sequelae are avoided if replacement therapy with levothyroxine is

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started within the first 3 months of life. Undiagnosed congenital hypothyroidism has become rare in industrialized countries owing to neonatal screening. Transient perinatal hypothyroidism may result when mothers are given iodine or iodine-containing contrast agents [24].

Euthyroid Sick Syndrome

Many severely ill patients without signs or symptoms of thyroid dysfunction have a low T_3 level or have T_3 and T_4 levels below normal range. Free T_4 is usually normal if measured by a reliable, sensitive assay, and TSH is also usually normal. This so-called euthyroid sick syndrome is not indicative of true tissue hypothyroidism, and replacement is unnecessary unless the TSH level becomes markedly elevated (>20 μU/mL) [32].

Thyroid Nodules and Thyroid Cancer

Benign thyroid nodules are frequently encountered in primary care. They are estimated to occur in 4–8 % of the adult population. In contrast, clinically significant thyroid cancer is infrequent, comprising only 1 % of all malignancies and ranking 35th among causes of cancer death. Clinically insignificant thyroid cancers are more common, with American autopsy studies revealing a prevalence of 6–13 % [33].

Health Risks and Family Issues

Providing cost-effective yet thorough management for patients with thyroid nodules represents a distinct challenge to family physicians (Fig. 3). Although thyroid nodules carry a low risk of mortality due to thyroid cancer, patients and their families must struggle with the knowledge that a potentially malignant growth is present. The anxiety produced by this fear not only causes stress in the patient but also has major implications for the family. Therefore, the evaluation should reveal adequate information not only to satisfy the physician but to alleviate the fears of patients and their family members.

Evaluation

Table 2 lists the findings that indicate high and moderate risks of cancer. When two or more of these factors are found, the probability of thyroid cancer is high. Laryngoscopy to evaluate vocal cord function is indicated, especially if any hoarseness or voice change has occurred. A history of neck irradiation increases the risk of both benign and malignant thyroid nodules. Multiple thyroid nodules suggest a benign process.

Laboratory Studies

Thyroid function tests and the TSH assay are useful for confirming the clinical impression of thyroid status. Thyrotoxic nodules are only rarely malignant [5, 34]. Measurement of antibodies to thyroid peroxidase is useful for identifying autoimmune thyroiditis when there is also diffuse enlargement of the gland. A calcitonin assay is important in patients with a family history of multiple endocrine neoplasia type II (MEN-II) or medullary carcinoma, as calcitonin is usually elevated under these conditions. Genetic

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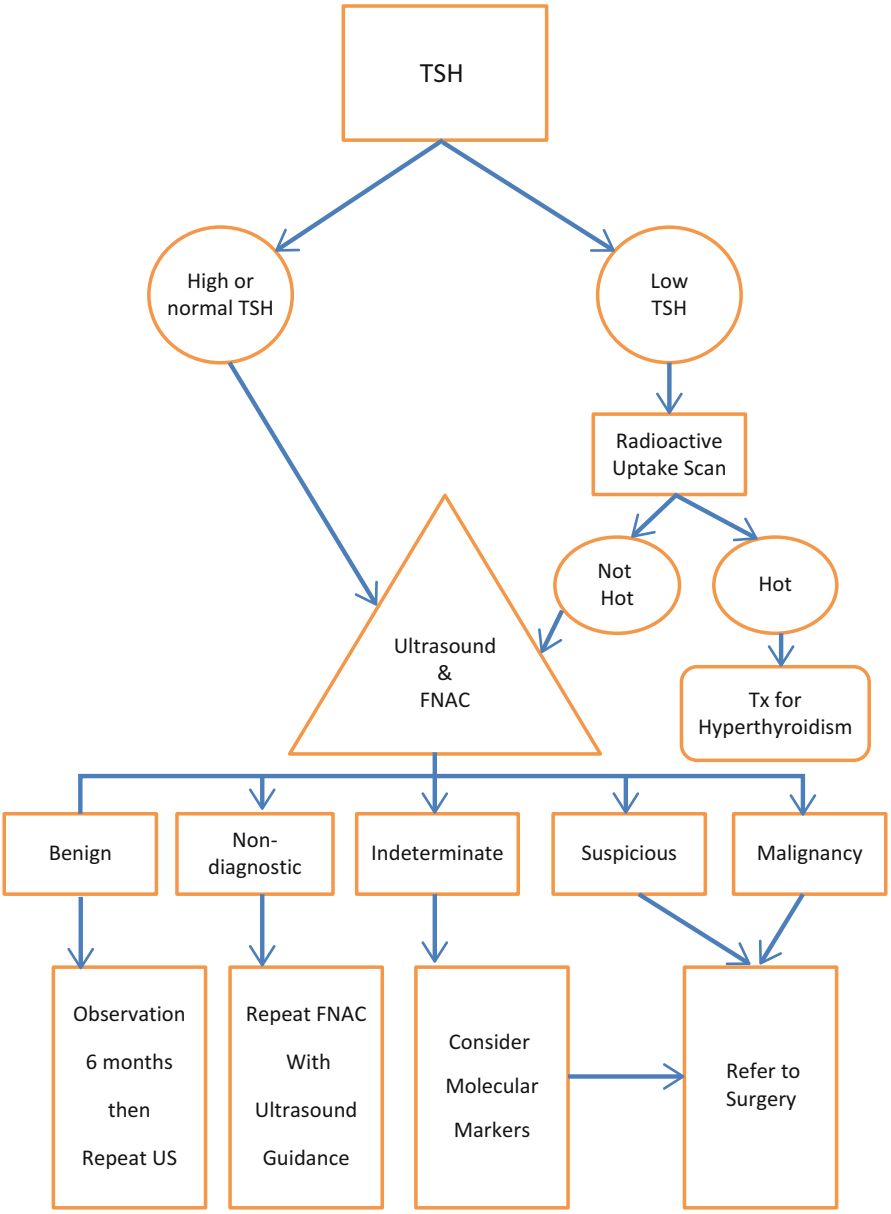

Fig. 3 Evaluation of thyroid nodule (palpable or incidental)

testing and calcitonin elevation may identify family members with this type of thyroid cancer before clinical manifestations appear [5, 29, 33].

Work-Up

The work-up of a solitary nontoxic thyroid nodule is outlined in Fig. 3. The evaluation begins with a TSH. Patients with a low TSH need a radionuclide thyroid scan. A palpable nodule that corresponds to an area of tracer uptake requires no cytologic evaluation; however, a thyroid ultrasound may be considered. According to the American Thyroid Association (ATA) Guidelines, all thyroid nodules or suspected thyroid nodules in patients with an elevated or normal TSH should have ultrasonography to document location, number, size, and appearance of the nodule(s) followed by fine-needle aspiration and cytology (FNAC) [34]. Other experts maintain that all nodules should be examined through ultrasound, regardless of the TSH [35]. FNAC has become the initial procedure of choice because it is the most accurate and

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Table 2 Clinical factors suggesting malignancy in thyroid nodules

High probability
Rapid growth of nodule
Vocal cord paralysis
Fixation to adjacent tissue
Enlarged regional lymph node(s)
Very firm nodule
Family history of multiple endocrine neoplasia type II (MEN-II) or medullary carcinoma
Distant metastases (lungs or bones)
Moderate probability
Age <15 years
Age >70 years
History of neck irradiation
Diameter of nodule >4 cm
Male sex and solitary nodule

most cost-effective [34]. The FNA technique is relatively simple and low risk [5, 33], and its sensitivity is reported to be more than 90 % [36, 37]. The most worrisome limitation of FNAC is a false negative that may cause a malignancy to be missed, although the false-negative rate has been less than 10 % in most studies and in one study as low as 0.7 %. There is particular difficulty differentiating follicular adenoma from follicular carcinoma with FNAC, as finding evidence of invasion is required to diagnose the latter. A skilled and experienced cytopathologist is required for reliable results.

Results of FNAC are classified into five categories: (1) malignant when malignant cells are identified, (2) benign when adequate benign glandular tissue is present, (3) nondiagnostic when the biopsy tissue does not meet specific criteria for cytologic adequacy, (4) indeterminate which can be a follicular neoplasm (Hurthle cell neoplasm) or atypia, and (5) suspicious for papillary thyroid cancer. Results read as nondiagnostic require the FNAC to be repeated using ultrasound guidance [36].

Ultrasonography can be used to determine if a thyroid nodule is solid or cystic, but this finding does not completely differentiate benign from malignant nodules. Studies have demonstrated that 9–14 % of cystic nodules contain cancer compared to 10–20 % of solid nodules being cancerous [34]. Cystic degeneration occurs in 25 % of papillary carcinomas; therefore, the characteristic appearance of the nodule on ultrasonography does not determine whether or not a biopsy is indicated. Ultrasonography may be used to monitor and follow the characteristics and size of a nodule and to evaluate for metastasis.

Management

The decision regarding when to remove a thyroid nodule surgically should take into account several factors, including clinical findings, availability of FNAC with cytopathologic support, degree of anxiety of the patient and family, and ability to have reliable long-term follow-up. ATA Guidelines are as follows: (1) Surgery is recommended for patients with FNAC results demonstrating malignant cells or suspicion for malignant cells. (2) Observation and serial ultrasound examinations 6–18 months are recommended for nodules with benign FNAC. Should the nodule increase in size, repeat FNAC or surgery is indicated. (3) Repeat the FNAC if the initial results are nondiagnostic. Consider surgery if the second FNAC is also nondiagnostic. (4) Consider surgery or repeat the FNAC for a persistent nodule after aspiration of a cyst. (5) Recurrent cystic nodules with benign cytology should be considered for surgery or percutaneous ethanol injection [34].

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Routine suppression of benign thyroid nodules with thyroid hormone replacement is not recommended in iodine-sufficient populations. Thyroid nodules associated with Hashimoto's thyroiditis have been shown to respond to suppression [5].

Thyroid Cancer

Thyroid cancer is divided into two main types: differentiated thyroid cancer (DTC) and poorly differentiated thyroid cancer. DTC arises from thyroid epithelial cells and accounts for the vast majority of thyroid cancer and is associated with a more favorable prognosis. Surgery is the treatment of choice for all thyroid carcinomas when excision is possible [34, 36].

Differentiated Thyroid Cancer Cell Types

1. Papillary carcinoma accounts for 85 % of all thyroid cancers. The tumor is slow growing, and there is good long-term survival if surgical removal is performed while the cancer is still confined to the thyroid gland. Papillary carcinoma spreads by lymphatic means.
2. Follicular carcinoma accounts for about 10 % of all thyroid cancers. It is slightly more aggressive than the papillary variety and spreads by the hematogenous route. A subcategory of follicular carcinoma is the Hurthle cell type, which is more aggressive and more common in iodine-deficient countries [34].
3. Medullary carcinoma accounts for only 2–5 % of thyroid cancers. Most of these lesions are sporadic, but some are familial; 20 % are part of the MEN-II syndrome, which has an autosomal-dominant inheritance pattern. The latter can be identified early with elevated calcitonin levels and genetic testing. Screening with these tests should be performed on all family members if MEN-II or familial medullary carcinoma is diagnosed. If medullary carcinoma is not diagnosed prior to a palpable mass being present, the cure rate is less than 50 % [33, 34, 38].

Undifferentiated Thyroid Cancer Cell Type

1. Anaplastic thyroid carcinoma is the most aggressive type but accounts for only 2–7 % of cases. It has the worst prognosis of any thyroid cancer, with a median survival time of 4–7 months and a 5-year survival rate of only 4 %.

Near-total or total thyroidectomy is the procedure of choice if the thyroid cancer is greater than 1 cm. Lobectomy may be appropriate for less than 1 cm, low-risk carcinomas in some patients [34]. Radioiodine ablation is recommended for patients with known residual tumor and probably also for those at high risk of recurrence. Some patients with anaplastic thyroid cancer will respond to combined radiation and chemotherapy after thyroidectomy [5].

Thyroid Disease During Pregnancy

Both hypothyroidism and hyperthyroidism can complicate pregnancy (see chapter ▶ Medical Problems During Pregnancy). Hypothyroidism causes anovulation and rarely coincides with pregnancy. When hypothyroidism occurs, it is associated with gestational hypertension, premature labor, and low birth

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weight. Monitoring and management of the pregnant patient with thyroid disease requires the use of trimester-specific reference ranges for TSH and serum free T4 [39].

Thyroid-binding globulin increases during pregnancy, and so total T_3 and T_4 increase as well. Her dose of L-thyroxine should be adjusted to maintain the TSH level in the normal range on a sensitive assay [39]. In general, the pregnant patient with prepregnancy hypothyroidism will require an increase in her L-thyroxine of about 30 %. A convenient way to increase her L-thyroxine dose is for her to take nine doses per week rather than seven. Her TSH should be monitored 4 weeks after a dosage change and every 4 weeks during the first half of her pregnancy. The TSH should be rechecked at least once between 26 and 32 weeks gestation. After delivery, the patient should resume her prepregnancy dose and have her TSH assessed 6 weeks postpartum [39].

Hyperthyroidism during pregnancy is relatively uncommon and caused by the same etiologies as in nonpregnant patients, with Graves' disease being the most common cause. Thyrotoxicosis may lead to spontaneous abortion, stillbirth, neonatal death, and low birth weight [39]. All patients with a suppressed TSH should have their serum free T4 determined. Antithyroid drugs, usually propylthiouracil during the 1st trimester, followed by methimazole during the 2nd and 3rd trimester are recommended for treatment in pregnant patients. In addition, propranolol and occasionally thyroid resection may be used for treatment [39]. Any use of radioactive iodine is contraindicated during pregnancy.

Postpartum thyroiditis is a transient autoimmune thyroid dysfunction that occurs within the first postpartum year (see chapter ▶ Postpartum Care). It is probably an exacerbation of a preexisting subclinical autoimmune thyroiditis [5, 40]. The true incidence is 5–10 %, although it is frequently underdiagnosed [37]. The most common complaints are depression, poor memory, and impaired concentration. The clinical course consists of a hyperthyroid phase (which may be absent), followed by a hypothyroid phase and eventually a return to euthyroid status. The diagnosis is usually made with a TSH measurement. Patients with antibodies to thyroid peroxidase and thyroglobulin are at increased risk of developing this syndrome [41]. Patients who have one episode of postpartum thyroiditis are at increased risk for recurrence with future pregnancies and may develop permanent hypothyroidism [40].

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Osteopenia and Osteoporosis

Katherine Reeve and Ryan West

Contents

Osteoporosis is a major health concern worldwide and within the United States. Approximately 9 % of U.S. 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 % 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

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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.

Risk Factors for Osteoporosis

Lifestyle	Family history	Genetic/Medical
Poor diet Low activity level Tobacco use Alcohol use	History of osteoporosis History of fractures	Menopause Caucasian or Asian ethnicity Endocrine disorders Certain medications

Lifestyle

Lifestyle choices can affect bone density. Excessive use of alcohol may decrease bone formation by suppressing osteoblastic function, which increases the risk of osteoporosis. Cigarette smoking has been associated with an increased risk for osteoporosis, although the direct link is not well established [6].

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 [7]. 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 medroxyprogesterone aceteate (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 [8].

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 [9].

Bone Densitometry Assessment

Arguably the most important evaluation for osteoporosis is determining the bone mineral density (BMD). The diagnosis of osteoporosis it made

Table 1 Indications for bone mineral density (BMD) screening

US Preventive Services Task Force[a]
Women ≥65
Women <65 with fracture risk equal to or greater than 65 year old white female
Men: insufficient evidence to determine benefit vs harm
International Society for Clinical Densitometry[b]
Women ≥65
Women 60–64 with fracture risk equal to or greater than 65 year old white female
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, 2011
[b]International Society for Clinical Densitometry. Osteoporosis Screening Guidelines, 2012

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 1).

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 generates a report that is interpreted by a radiologist, endocrinologist, or other physician that has been certified to interpret the results. In the report both a T score and a Z score are given. The T score is defined as the number of standard deviations above or below the mean BMD. It is important to note that the T score is not adjusted for age, gender, or race and is instead compared to the mean BMP for a young Caucasian female. The Z score, however, is the number of standard deviations above or below the mean and 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 [10]. 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, which is adjusted for age, gender, and race, should be used instead [11]. 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 and include 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 is based of 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 as well if available but is not needed to generate the 10 year risk. There is a calculator

available online at www.shef.ac.uk/FRAX. It is often included on DXA reports [12]. This information can help guide management and may indicate the need for earlier treatment in patients with osteopenia (see Pharmacological Treatment section below).

Diagnosis

The diagnosis of osteoporosis is made primarily from bone mineral density using the 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 less than −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 less than 2.0 standard deviations below normal adjusted for age as reflected by a Z score of less than −2.0 [10]. 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.

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

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 1,200 mg/day. For adult men, it is slightly lower at 1,000 mg/day [13]. 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 [14]. 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 2). The National Osteoporosis Foundation (NOF) differs slightly. NOF recommends 400–800 IU for those under age 50 and a higher intake of 800–1,000 IU for those over age 50 [15]. Patients with a documented Vitamin D deficiency should be treated with 50,000 IU of Vitamin D2 (ergocalciferol) for 8 weeks followed by a maintenance dose of 1,000 IU of Vitamin D3 (cholecalciferol) daily. The treatment goal is a serum vitamin D level greater than 30 ng/ml.

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. Maintaining a healthy and

Table 2 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	700–1,300	400–600
14–18 years	1,300	600
Adult women		
Pregnant or lactating		
14–18 years	1,300	600
19–50 years	1,200	600
Other		
51–70 years	1,200	600
71+ years	1,200	800
Adult men		
19–70 years	1,000	600
71+ years	1,200	800

Adapted from the National Institutes of Health Recommendations on Calcium and Vitamin D 2011
[a]Calcium recommendations in mg/day
[b]Vitamin D recommendations in IU/day

active lifestyle may also reduce the risk of falls, which in turn may reduce the risk of fractures. Exercise is recommended as a safe and effective way to reduce bone loss [16].

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 increased 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 treatment and prophylaxis of osteoporosis include bisphosphonates, calcitonin, hormone therapy, estrogen agonists/antagonists, parathyroid hormone (PTH), and the RANK Ligand inhibitor Denosumab.

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 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. 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 the patient should be advised to take the medication with a full glass of water and remain upright for 30 min.

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. The 70 mg dose/week may increase compliance as it is dosed once weekly and also has been shown to have decreased 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 an oral medication. The recommended dose is 150 mg taken every month.

Zoledronic Acid (Reclast)

Zoledronic acid is the only 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 dosed just once yearly.

Hormonal

Hormone Replacement Therapy (HRT)

Hormone replacement therapy is FDA approved for the prevention of osteoporosis in women and has been shown to decrease vertebral and hip fractures by 34 % [17]. It is available in oral and transdermal preparations.

Safety issues continue to be controversial with HRT with possible increased risk of myocardial infarction, stroke, breast cancer, pulmonary embolus, and deep vein thrombosis. Given these risks, it is best to consider nonhormonal treatments for primary treatment of osteoporosis. It may be a reasonable treatment option for patients who also have moderate to severe postmenopausal symptoms. If it is used, it should be used for at the lowest effective dose for the shortest duration possible.

Estrogen Agonist/Antagonists (Formerly Known as Selective Estrogen Receptor Modulators (SERMs))

Estrogen Agonist/Antagonists work by acting on estrogen receptors within the bone to prevent resorption and have been shown to increase BMD and decrease fractures in postmenopausal women. However, they are less effective than bisphosphonates and carry all the risks of HRT. They are therefore considered second-line treatments. They do have one advantage in that they may decrease the risk for breast cancer. Raloxifine is the preferred agent in this category and has been shown to decrease the risk of breast cancer. It is a reasonable alternative for postmenopausal women who cannot tolerate bisphosphonates or who 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 [18].

Calcitonin

Calcitonin is an alternative treatment method for osteoporosis. It inhibits by bone resorption by binding to osteoclasts. It is available in several forms including intranasal, intramuscular, and subcutaneous. The nasal dosing is usually preferred as it can easily be dosed at home without

needing an injection and tends to have a lower side effect profile. One of the benefits of calcitonin is its analgesic effect. Studies have shown that when taken after a vertebral fracture, pain has been significantly reduced at 2, 3, and 4 weeks. However, no benefit has been shown when used for chronic pain [19].

Calcitonin has been shown to increase bone mass and prevent fractures when compared to placebo. However, when compared to bisphosphonates, it is inferior at both increasing bone mass and preventing fractures [20]. For this reason, it is not considered first-line treatment, but is a reasonable alternative if a patient is unable to tolerate bisphosphonates or for short-term analgesic use following an osteoporotic fracture.

Parathyroid Hormone (PTH)

PTH works as an anabolic agent by stimulating osteoblastic activity. It is currently the only anabolic agent that is FDA approved for the prevention and treatment of osteoporosis. 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. The risk of osteosarcoma is controversial as it has only been shown in animal studies and has not been confirmed in any human trials [21]. However, given the possible risk the FDA currently recommends limiting PTH therapy to 2 years until further longitudinal studies have been completed.

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 in similar rates to that of 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 [22].

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, adequate calcium and vitamin D intake, and avoidance of tobacco and excessive alcohol use. Obtaining a detailed history is essential to identify patients that may be at increased risk of developing osteoporosis. Universal screening guidelines exist for all women greater than 65 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. Other pharmacological options are available for patients who cannot tolerate bisophosphonates or have other special considerations.

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Selected Disorders of Nutrition

Douglas J. Inciarte

Contents

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. Even though Rickets 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.

Vitamin D deficiency in adults can increase the risk of osteopenia and osteoporosis and can cause

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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.

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 that this measurement reflects total vitamin D from dietary intake and sunlight exposure, as 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 increase risk for harm. Once intakes surpass 2,000 mg 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 paresthesias or numbness and gait problems [11, 12].

Physical examination may reveal pallor, edema, pigmentary changes in the skin, jaundice, or neurologic defects such as impaired vibration 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 methylmalonic acid 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 anti-parietal 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.

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) [18].

In child-bearing women, a high dose of folic acid supplement reduces the incidence of recurrent neural tube defects by 70 % [17].

Folate deficiency is also common in the 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 a global health problem and continues to be the top cause of anemia affecting more than two billion people worldwide. It is prevalent in pediatrics and in premenopausal women in both low-income and developed countries [21]. The estimated prevalence of iron deficiency worldwide is twice as high as that of iron-deficiency anemia.

The reported prevalence of iron deficiency in the absence of dietary fortification is approximately 40 % in preschool children, 30 % in menstruating girls and women, and 38 % in pregnant women [22, 23].

In developing countries, iron deficiency and iron-deficiency anemia are the results of lack of dietary intake, loss of blood due to intestinal parasite colonization, or both.

In first-world countries, certain eating habits such as vegetarian diet or no intake of red meat and pathologic conditions such as acute gastrointestinal bleeding or malabsorption are the most common causes. Other causes are sprue, atrophic gastritis, *H. pylori* infection, gastrectomy, and gastric bypass procedures.

The diagnosis of iron deficiency is the same as for any suspected anemia: complete blood count, red blood cell indices, and examination of the peripheral blood smear. A low serum ferritin is diagnostic of iron deficiency. If the diagnosis of iron deficiency is suspected, then a therapeutic trial of iron administration to provide both confirmation of the diagnosis and therapy is indicated. The presumptive diagnosis is made if there is a positive response to a trial of oral iron replacement, characterized by a modest reticulocyte count increase after 5–7 days, followed by an increase in hemoglobin until approximately 3 weeks until the serum ferritin and hemoglobin concentration return to normal.

The treatment of iron deficiency consists of oral administration of iron sulfate (which is the most frequent presentation in the United States). A daily dose for adults with iron deficiency is 100–200 mg of elementary iron and that for children is 3–6 mg per kilogram of body weight of a liquid preparation; for both groups, the supplement should be administered in divided doses without food. Vitamin C ingestion may improve iron absorption. Long-term use of oral iron is limited by side effects, including nausea,

vomiting, constipation, and metallic taste; these side effects are frequent and, although not severe, are often worrisome to patients.

In severe cases including malabsorption or blood loss, patients will need intravenous iron or transfusion in the face of acute blood loss. The intravenous route is the preferred route when a rapid increase in hemoglobin level is required when iron replacement cannot be accomplished via the oral route.

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 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 2007–2008 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, non-supplemental 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].

Our conclusion is 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 (hypophysis) has two distinct parts: an anterior lobe (adenohypophysis) and a posterior lobe (neurohypophysis), which have different embryological origins. There is also a vestigial intermediate lobe. The neurohypophysis is not a true gland. Instead, macroneurons of the hypothalamus project to the posterior pituitary and release into capillary beds either oxytocin or vasopressin that are similar 9-amino-acid peptides. Vasopressin is also known as arginine vasopressin (AVP), antidiuretic hormone (ADH), and argipressin. The adenohypophysis is a true gland containing different cell types that secrete several discrete hormones (see Table 1). The production and pulsatile release of these hormones are under the control of neurons of the hypothalamus that secrete regulatory hormones (e.g., gonadotropin-releasing hormone, GnRH) that are transported to the adenohypophysis by a tiny portal vein system. Excess secretion of anterior pituitary hormones may be due to hypothalamic stimulation, loss of hypothalamic inhibition, or a hormone-secreting adenoma. If an adenoma is secretory, usually only one hormone is produced, which is typically prolactin, growth hormone (GH), or adrenocorticotropic hormone (ACTH), which is also known as cosyntropin.

Hyperprolactinemia and Galactorrhea

Prolactin is a 198-amino-acid hormone that is required for lactation but not breast development. Hyperprolactinemia may be noted during the evaluation of breast discharge, menstrual disorders, infertility, or impotence. The hypothalamus inhibits pituitary prolactin release. Any condition which impacts the hypothalamus or the pituitary stalk causing hypopituitarism may lead to hyperprolactinemia.

The pituitary may secrete prolactin in response to stimulation of the nerves innervating the breast. This may be due to trauma, scars, breast implants, neoplasm, herpes zoster, or nipple stimulation secondary to clothing or foreplay. Pregnancy, hypoglycemia, stress, food ingestion, and sleep are physiological causes of prolactin release. Certain medications have been implicated as the cause of hyperprolactinemia, including opioids, estrogens, verapamil, alpha methyldopa, risperidone, selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, monoamine oxidase inhibitors, cimetidine, metoclopramide, and dopamine receptor antagonists [1, 2]. Chronic diseases such as renal failure, cirrhosis, and hypothyroidism may also lead to increased prolactin secretion.

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Table 1 Hormones of the Adenohypophysis (anterior pituitary)

Pituitary cell type (staining characteristics)	Hormone(s) secreted	Target site	Clinical consequence of excess	Clinical consequence of 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 syndrome	Adrenal insufficiency
	β-Lipoprotein	Skin	Hyperpigmentation	Hypopigmentation
Thyrotrophs (chromophobic)	TSH	Thyroid	Hyperthyroidism[a]	Hypothyroidism
Gonadotrophs (chromophobic)	FSH, LH	Females: ovaries Males: testes	Precocious puberty	Delayed puberty, infertility, loss of secondary sexual characteristics

[a]Secondary hyperthyroidism is a rare condition. Chromophobe adenomas are usually nonsecretory
GH growth hormone, *ACTH* adrenocorticotropin hormone, *TSH* thyroid-stimulating hormone, *FSH* follicle-stimulating hormone, *LH* luteinizing hormone

Clinical Presentation

Women frequently present with oligomenorrhea, infertility, galactorrhea, vaginal dryness, and dyspareunia. Men may present with hypogonadism, erectile dysfunction, infertility or gynecomastia, occasionally with galactorrhea. They tend to present with headache and visual symptoms due to increased incidence of macroadenoma [3].

Diagnosis

A complete medical history including medications is important. Information about chronic medical issues such as renal failure, hepatic failure, and hypothyroidism should also be elicited as these conditions may lead to hyperprolactinemia.

In women of childbearing age, pregnancy should be excluded. Other initial laboratory tests include thyroid, renal, and hepatic function studies. Prolactin levels should be obtained. Normal prolactin levels for nonpregnant women are 2–29 mIU/L and 2–18 mIU/L in men. Visual field testing should be performed in patients presenting with complaints of headache or visual disturbance.

Magnetic resonance imaging (MRI) determines tumor size and excludes presence of other sellar and stalk lesions [3]. Pituitary adenomas are the most common cause of hyperprolactinemia [4]. Prolactinomas are the most common pituitary adenomas and are divided into microadenomas (<1 cm) and macroadenomas (>1 cm). There is evidence to suggest that patients who do not have macroadenoma, enlarging microadenoma, infertility, persistent galactorrhea, gynecomastia, testosterone deficiency, oligo/amenorrhea, or acne/hirsutism may not require intervention. Their physicians may opt to monitor symptoms, prolactin levels, and interval MRI. The data are not clear regarding precise MRI intervals for follow-up [3].

Management

Medication-induced hyperprolactinemia should be addressed by removal of the causative agent. The medication should be discontinued for 3–4 days, and an alternative agent should be found. Dopamine agonists are the drugs of choice for treatment of hyperprolactinemia due to macroprolactinomas or to

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Table 2 Selected causes of hypopituitarism

Neoplastic causes
Adenoma
Craniopharyngioma
Metastases
Ischemic causes
Sheehan syndrome (postpartum pituitary necrosis)
Diabetic microvascular disease
Temporal arteritis
Granulomatous causes
Sarcoidosis
Wegener's granulomatosis
Hand-Schüller-Christian syndrome
Developmental causes
Congenital malformation
Developmental cyst
Hydrocephalus
Infectious causes
Tuberculosis
Syphilis
Fungal disease
Meningitis, abscess
Physical causes
Traumatic Brain Injury
Radiation therapy
Surgery, hypophysectomy
Toxic atmosphere (vincristine)
Miscellaneous causes
Pituitary apoplexy
Cavernous sinus thrombosis
Primary empty sella syndrome
Immunologic (lymphocytic hypophysitis)
Idiopathic (occasionally familial)

microadenomas that require intervention [3]. Bromocriptine and cabergoline are derived from ergot and may restore prolactin levels, shrink adenomas, and increase bone density. Recent studies have found that cabergoline produces fewer side effects and is more effective at normalizing prolactin levels than bromocriptine [5]. One risk of cabergoline is an increased association with cardiac valvular disease. Trans-sphenoidal surgery remains the mainstay of treatment for the majority of macroadenomas; however, 10 % of adenomas may recur after surgery [6].

Hypopituitarism

Hypofunction of the pituitary is a rare disorder that may be either partial or complete (panhypopituitarism). It is caused by a number of disorders that disturb the gland directly (primary hypopituitarism) or the hypothalamus (secondary hypopituitarism) (see Table 2).

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Table 3 Selected causes of precocious puberty

Central precocious puberty
True precocious puberty
Central nervous system lesions
Gonadotropin-secreting tumor
Profound hypothyroidism
Chronic adrenal insufficiency
Peripheral (pseudo) precocious puberty
Girls
Ovarian tumor
Follicular cysts
Exogenous estrogens
Boys
Testicular tumor
Autonomous Leydig cell function
Exogenous androgens
Either
Polyostotic fibrous dysplasia
Adrenal tumor
Adrenal hyperplasia

Clinical Presentation

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. Symptoms may develop abruptly (as in the Sheehan syndrome) or slowly (as with a slow-growing nonsecretory adenoma). Partial loss of pituitary function might mimic primary failure of the target site. 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 diabetes insipidus (DI).

Diagnosis

If the patient is viewed as a whole, the diagnosis is suggested by the clinical history and examination and can be confirmed by simultaneously measuring serum pituitary and target gland hormone levels [7]. MRI is the preferred method for evaluating hypothalamic and pituitary anatomy.

Management

Treatment is aimed at the underlying condition and replacement of target gland hormones. 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

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of abnormality in growth hormone production, which may improve after 1 year [8]. These patients should wear a medical identification bracelet or necklace.

Neuroendocrine Disorders of Water Balance

Endocrine diseases may present with abnormalities of water balance: hyponatremia, hypernatremia, polyuria, or polydipsia. Body water and osmotic homeostasis are balanced under physiological conditions by a sensitively regulated vassopressin system essentially depending on two determinants: the serum osmolality and arterial blood volume [9]. Thirst is an important backup mechanism, becoming indispensable in the moment when pituitary and renal mechanisms fail to maintain body fluid homeostasis. Addison disease causes hyponatremia due to excessive sodium excretion. The syndrome of inappropriate secretion of ADH (SIADH) may result from disruption of normal feedback to neurohypophyseal system.

Polydipsia

Primary Polydipsia

Primary polydipsia (PP) results from an excessive fluid intake ingested over an extended period of time and not from deficient vassopressin secretion or activity. An excessive consumption of fluids results in excessive body fluid, decreased serum osmolality, and suppressed vassopressin release. PP comprises patients with a defective thirst mechanism or with increased thirst sensation (dipsogenic DI) and patients with a more unknown motive for polydipsia frequently associated with psychiatric disorders (psychogenic polydipsia). The subsequent increase in water excretion compensates for the high fluid intake, and the tonicity stabilizes at a new set point around the osmotic threshold for vassopressin secretion. Therefore, despite intact pituitary and renal function, patients with PP share essential characteristics of DI. Because dipsogenic DI can be caused by the same hypothalamic lesions as found in central DI, it is essential to perform cranial MRI (cMRI) scans in all patients with PP before idiopathic or psychiatric illness can be diagnosed. PP may also have an iatrogenic origin, either due to drug intake associated with oral dryness of anticholinergic medications or due to the medical advice to increase fluid intake for certain health benefits.

Secondary Polydipsia

Secondary polydipsia is protective in patients with polyuria from any cause. When access to water is limited, dehydration, hypernatremia, and death can result. It is difficult or impossible to determine the underlying cause among psychiatric patients, although a water deprivation test could be helpful. The clinician should also search for some other underlying diseases and should not automatically assume that psychogenic polydipsia is the cause of polyuria or hyponatremia in a psychiatric patient. In such situations, the clinician could evaluate the patient for hypopituitarism biochemically and radiographically. Functional evaluation of the thyroid, adrenals, and kidneys may also prove useful.

Polyuria and Central Diabetes Insipidus

Polyuria may be due to central diabetes insipidus (DI), nephrogenic DI, an osmotic diuresis, or primary polydipsia. Osmotic diuresis of diabetes mellitus resulting in polyuria is also seen with poorly resorbed solutes (e.g., mannitol, sorbitol, and urea).

Central DI is caused by a deficiency of vasopressin either through loss of the large hypothalamic neurons that synthesize vasopressin or via destruction of the capillary beds of the posterior pituitary. Acquired central DI mostly results from trans-sphenoidal surgery of the pituitary or head trauma

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[9]. Central DI may be partial or complete, transient or permanent, associated with other pituitary deficiencies or the sole abnormality. It is produced by the disorders causing hypopituitarism but can also be inherited as an X-linked trait. A transient form is associated with pregnancy.

Clinical Presentation

Polyuria and polydipsia are the only findings in the idiopathic form, but acquired central DI may also present with the symptoms and signs of the associated pituitary lesion. Depending on the underlying etiology, the onset of central DI may be gradual or abrupt. Large volumes (>30 mL/kg) of dilute urine (specific gravity <1.010, osmolality <300 mOsm/L) are excreted over a 24-h period. Nocturia is usually present.

Diagnosis

A water deprivation test is used to distinguish DI from other causes of polyuria. In a controlled setting, water intake is restricted, and the weight and the sodium and osmolarity of the plasma and urine are measured hourly. The patient should not be allowed to lose more than 5 % of body weight. Dilute urine in the face of concentrated serum suggests DI. Then, vasopressin is administered to differentiate central DI from nephrogenic DI. Newly available assay for copeptin, the C terminus of the vasopressin precursor which is surrogate for endogenous plasma vasopressin, holds promise as an easy-to-measure response to an appropriate osmotic stimulus. It offers the potential for higher diagnostic specificity and simplification of the differential diagnostic protocol of DI. T1-weighted MRI studies of the posterior pituitary within the sella turcica may also help to distinguish central DI from PP [9].

Management

The treatment of central DI is directed at diagnosing and treating the underlying cause if possible. Intranasal synthetic analogues of vasopressin are used to treat central DI, though absorption may be erratic with a common cold or allergic rhinitis. Partial central DI may be treated successfully with diuretics (thiazides) or ADH-releasing drugs (e.g., chlorpropamide, carbamazepine). Medical identification should be worn by patients.

Disorders of Secondary Sexual Characteristics

Secondary sexual characteristics are initially expressed at puberty and are maintained in adults by the sex hormones.

Normal Puberty

Puberty is the process leading to physical and sexual maturation that involves the development not only of secondary sexual characteristics but also skeletal growth, alterations in lean body mass, and psychological changes. Normal puberty consists of two main endocrinologic events: adrenarche and gonadarche. Adrenarche is the increased secretion of adrenal androgens that normally occurs in both genders between 6 and 8 years of age, usually preceding gonadarche. It is associated with bone growth and changes in pilosebaceous units. Although the adrenals account for some pubic hair growth, the biological role of adrenarche is not completely understood [10]. Gonadarche is initiated by the hypothalamus. Episodic secretion of GnRH by the hypothalamus results in the pulsatile secretion of the gonadotropin follicle-stimulating hormone (FSH) and luteinizing hormone (LH) by the anterior pituitary.

In boys, LH stimulates testosterone secretion by the Leydig cells, and after spermarche, FSH supports the maturation of spermatozoa. The process of puberty initiates with testicular enlargement and is

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followed by the appearance of pubic hair and enlargement of the penis. Skeletal growth is a late event of male puberty.

In girls, FSH stimulates follicle formation and estrogen secretion. After the onset of ovulation, LH stimulates the development of the corpus within a ruptured graafian follicle. In girls, puberty is heralded by breast development and skeletal growth, followed by the appearance of pubic and axillary hair and then menarche. Recent data suggests that the average age of menarche in the USA, which previously was stable at 12.8 years, has decreased [11, 12]. The change is likely due to the obesity epidemic. Current evidence suggests that pubertal development in girls is associated with body mass index [13].

Precocious Puberty

Precocious puberty may be due to CNS processes or peripheral processes (See Table 3). Central precocious puberty is due to the premature production of gonadotropins. In young children, the process is likely to be pathological. Peripheral precocious puberty is defined by the early appearance of sex hormones. A clinician can distinguish between central and peripheral precocious puberty by order of appearance of sexual characteristics and onset of puberty in family members. Height, weight, Tanner stages of breast development, axillary and pubic hair growth, and genitalia are documented. Radiographs of the left wrist for bone age may be taken. A difference of greater than two standard deviations is considered abnormal.

The treatment of central precocious puberty, which is considered gonadotropin-releasing hormone (GnRH) dependent, is with long-acting GnRH agonists [14]. The agonists maintain constant serum levels of GnRH activity, which supersedes the pulsatility of endogenous GnRH [15]. Options for treatment include depot injections of leuprolide acetate (Lupron Depot-Ped®) administered every 4 weeks, extended depot leuprolide acetate (Lupron Depot-Ped 3 Month®) administered every 3 months, and the annual histrelin subcutaneous implant (Supprelin LA®) [15]. These interventions may be utilized, particularly in girls under age 6 years to preserve adult height potential. GnRH therapy may reduce gonadal sex steroid production within 2–4 weeks in girls and within 6 weeks in boys [14]. The treatment of peripheral precocious puberty depends on the etiology. For example, girls with McCune-Albright syndrome may be treated with the estrogen receptor antagonist fulvestrant (Faslodex®). Boys with familial testotoxicosis have been treated "off-label" with medroxyprogesterone or with flutamide and letrozole [15].

Delayed Puberty

Boys who have not demonstrated testicular enlargement by the age of 14 or for whom 5 years or more have passed between the initial and complete growth of the genitalia have delayed puberty. Girls who have not developed breast buds by the age of 13 or who exhibit primary amenorrhea (passage of 5 years or more between the appearance of breast buds and menarche) have delayed puberty. An appropriate initial assessment consists of a medical history, a complete physical examination with particular attention to the timing of pubertal milestones, and a graph of height and weight. A radiograph of the left wrist for bone age should be obtained. Children with delayed puberty may then be grouped according to the initial assessment: those who appear normal, those who appear to have chromosomal abnormalities (e.g., Turner syndrome in girls, Klinefelter syndrome in boys), and those who appear to have a chronic disease (e.g., hypopituitarism, malignancies, chronic infections, malnutrition, anorexia nervosa). Those who seem normal except for pubertal delay may have a constitutional pubertal delay, primary hypogonadism (e.g., congenital defects, tumors, injuries, infections), or secondary hypogonadism (i.e., gonadotropin deficiency). Appropriate diagnostic tests include serum FSH, LH, estradiol (in girls), or testosterone (in boys); a GnRH stimulation test; and MRI if a CNS lesion is suspected.

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Hypogonadism in Adults

Adults may present to their physicians with infertility and loss of secondary sexual characteristics. In men, primary hypogonadism is most often caused by exposure to physical agents (cytotoxic drugs, radiation, or alcohol), infections (mumps), or trauma requiring castration [16]. Women lose gonadal function following oophorectomy and during menopause, but ovarian failure before the age of 40 is considered premature. The serum pituitary gonadotropins (i.e., FSH and LH) are elevated with gonadal failure. Sex hormone replacement therapy can restore secondary sexual characteristics but not fertility. Unexplained loss of secondary sexual characteristics should prompt an evaluation for secondary hypogonadism (i.e., hypopituitarism) consisting of hormonal studies of the hypothalamic-pituitary axis and possibly MRI of the sella.

Hirsutism and Virilization

Excessive hair growth leads many women to seek medical advice. The significance of this complaint can range from a minor cosmetic issue to the early sign of an adrenal adenocarcinoma. The clinician must determine if the clinical presentation is due to an idiopathic etiology, nonandrogenic factors, or androgen excess. Medications which promote increased hair growth include cyclosporine, minoxidil, diazoxide, dexamethasone, phenytoin, and streptomycin. These often promote vellus hair growth, which is soft and lightly pigmented. Hirsutism is the excessive growth of androgen-dependent hair on the face, axilla, chest, and suprapubic areas of women, and it may be physiological. It is a common presentation of the polycystic ovarian syndrome. The use of androgens for "body sculpting" may lead to hirsutism. Virilization refers to the androgen-dependent masculinization of women and is characterized by clitoromegaly, deepening voice, increased muscle mass, temporal balding, and hirsutism. When virilization is accompanied by defeminization (decrease breast size and vaginal atrophy), it is always pathological.

Diagnosis

A systematic approach should be efficient, safe, and cost effective [17]. A detailed history about onset of hirsutism, weight changes, menstrual history, medications including illicit androgen use, and balding can be helpful as is a family history of similar presentations. The examination should evaluate the presence of terminal hair on cheeks, axillae, chest, and abdomen to determine if the pattern of hair growth is distributed in a male hair pattern and involves terminal hairs which are long, pigmented, and coarse. The Ferriman-Gallwey score identifies hair growth in 11 areas and may be used for continued evaluation. A score greater than 8 confirms the presence of hirsutism. The examination must also determine if the signs of virilization or defeminization are present. The presence of ambiguous genitalia is suggestive of the virilizing forms of congenital adrenal hyperplasia.

Since androgen-mediated hirsutism is almost never associated with a normal menstrual pattern, women with hirsutism and oligomenorrhea should have plasma testosterone measured. If the testosterone result is abnormal ($>$200 ng/dL), MRI examination of the adrenal glands and pelvic organs should be performed to look for a mass. If the testosterone result is mildly elevated but $<$ 200 ng/dL, then an ACTH stimulation test can be performed to differentiate adrenal causes (e.g., 21-hydroxylase deficiency) from other causes (e.g., "obesity-related" insulin resistance).

Management

Cosmetic treatments include shaving, plucking, and waxing. Electrolysis, thermolysis, nonlaser light, and lasers are expensive treatment options. Eflornithine is a topical medication used twice daily to slow hair growth. Patients can expect improvement in 2 months. Cessation of the medication results in regrowth of the hair [18]. The diuretic spironolactone is a potent antiandrogen that has been used off label for hirsutism in doses of 100–200 mg per day [19, 20]. Spironolactone is associated with fetal genital development

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abnormalities. Flutamide, an androgen receptor blocker, has also been used off label and has multiple side effects, including discolored urine and liver enzyme abnormalities. Metformin and troglitazone can reduce insulin resistance among those women with polycystic ovaries [21, 22] but has potential for side effects. Birth control pills and long-acting GnRH agonists may suppress the hypothalamic-pituitary-ovarian axis.

The Parathyroids and Calcium Metabolism

The parathyroids are four tiny glands located in the neck close to the thyroid that secrete parathormone (PTH). PTH and vitamin D (a prohormone) are the principal regulators of calcium and phosphate metabolism. The action of parathormone includes (1) liberation of calcium from the bone through activation of osteoclasts; (2) enhancement of resorption of calcium from the renal tubules, thus decreasing renal calcium loss; (3) stimulation of intestinal absorption of calcium directly and by promoting the production of renal calcitriol; and (4) inhibition of the renal reabsorption of phosphate. Calcitonin produced in response to hypercalcemia by perifollicular cells of the thyroid inhibits bone resorption by a direct action on osteoclasts. Excessive secretion of calcitonin does not usually cause hypocalcemia. It is rare in patients with thyroid medullary carcinoma, which typically secretes large amounts of calcitonin.

Hypoparathyroidism and Hypocalcemia

Characteristic features of hypoparathyroidism are hypocalcemia and hyperphosphatemia. Hypomagnesemia and low or inappropriately normal levels of PTH may also be observed. Hypoparathyroidism usually follows surgical removal of the parathyroids. Target organ unresponsiveness to PTH can be inherited (DiGeorge syndrome) or idiopathic, which occurs sporadically. Intestinal diseases or poor dietary intake are important causes because maintenance of appropriate serum calcium levels requires intestinal absorption of calcium. Vitamin D deficiency, hypomagnesemia, and pancreatitis may also lead to hypocalcemia. Hypocalcemia can occur with renal tubular acidosis or renal failure. Autoimmune polyendocrine syndrome type 1 (APS-1), which is a multiorgan autoimmune disorder, is also an important cause in which autoantibodies are detected against NALP5 (expressed in cytoplasm of parathyroid chief cells) [23].

Clinical Presentation

The symptoms and signs of hypoparathyroidism are primarily neurological: paresthesia, Chvostek's sign, carpopedal spasm, tetany, delirium, and seizures. Symptoms are related to the degree of hypocalcemia. Patients with mild symptoms might mimic psychiatric disorders such as dementia, depression, or psychosis. ECG changes such as prolonged QT interval may be noted.

Diagnosis

In the frail and older adult population, hypoalbuminemia is a common cause of abnormally low serum calcium value. Measured total serum calcium decreases by 0.8 mg/dl for every 1 g/dL decrease in total serum protein. If after this correction is made, the serum calcium is still abnormally low and hypoparathyroidism is suspected, a serum PTH assay should be obtained. Inappropriately elevated PTH values are found with hypocalcemia associated with pancreatitis, hyperphosphatemia, and vitamin D deficiency (secondary hyperparathyroidism).

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Management

Treatment is aimed at the underlying disease if possible. Calcium and vitamin D are the cornerstones of replacement therapy. One gram of calcium carbonate can be taken with each meal and increased to 9–12 g/day (constipation can be a problem). A single administration of vitamin D3 alone with a mean dose of 2.04 μg/day is not only safe but also an easy and cost-effective regimen [24]. Dietary restriction of proteins decreases phosphorus absorption, which is an important factor in management of hypocalcemia. Intravenous calcium is required for acutely ill patients.

Hyperparathyroidism and Hypercalcemia

Primary hyperparathyroidism causes hypercalcemia through increased bone resorption and is due to an autonomously functioning benign adenoma 80 % of the time. Idiopathic or familial parathyroid hyperplasia accounts for most of the rest. Multiple adenomas, carcinoma of the parathyroids, or ectopic production of the PTH by a malignancy are rare causes. Other causes of hypercalcemia due to increased bone resorption of calcium include metastatic cancer, Paget's disease, hyperthyroidism, and prolonged immobilization. Hypercalcemia may also occur because of decreased renal excretion of calcium (thiazide diuretics, lithium) or increased absorption of calcium from the gut (sarcoidosis, vitamin D intoxication). Prolonged tourniquet use can cause measured serum calcium levels to appear elevated.

Clinical Presentation

Hyperparathyroidism may present as hypercalcemia discovered via routine multichemistry testing associated with the subtle psychological symptoms of anxiety, indecision, loss of energy, excessive worry, and irritability. Hypercalcemia may also present as an acute or chronic illness with lethargy, nausea, vomiting, polydipsia, polyuria, impaired renal function, nephrocalcinosis, muscle atrophy, or bradycardia. A short QT interval may be noted on the electrocardiographam (ECG), and severe hypercalcemia can produce ECG changes mimicking an acute myocardial infarction [25]. Thirteen percent (13 %) of the cases of acute pancreatitis during pregnancy are associated with hyperparathyroidism due to a parathyroid adenoma compared to 0.4 to 1.5 % in the general population [26].

Diagnosis

Elevated serum calcium levels are more than 10.5 mg/dL. Because almost half of total serum calcium is protein bound, adjustment may be required if a variation in the serum protein level also exists. An increase of protein by 1 g/dL raises the measured total serum calcium by about 0.8 mg/dL. Because serum calcium levels may fluctuate, results that are minimally elevated (10.5–11.5 mg/dL) should be repeated several times; the average value, not the lowest, is then used for clinical decision-making. If malignancy is suspected, a chest radiograph, a bone scan, and in men the serum prostate-specific antigen (PSA) and alkaline phosphatase levels are useful tests. Patients with Paget's disease have characteristic radiographs of bones, and patients with sarcoidosis or tuberculosis may have abnormal chest radiographs. If hyperparathyroidism is suspected, measuring serum PTH level is essential.

Management

The key to management of hypercalcemia is diagnosis and treatment of underlying disease. For patients with minimal symptoms, maintenance of hydration, dietary restrictions of calcium intake, and loop diuretics are recommended (thiazide diuretics are contraindicated because they enhance renal reabsorption of calcium). Chronic therapy involves oral glucocorticoids in the lowest effective dose for patients with malignancies or sarcoidosis and oral phosphates. Acutely symptomatic patients may require treatment in a hospital setting. Many of these patients can be managed conservatively. Surgical treatment of patients with symptomatic or mildly symptomatic hyperparathyroidism is controversial, but it is

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required for symptomatic patients with parathyroid adenomas or hyperplasia. Emergency treatment of severe tumor-induced malignant hypercalcemia with a combination of calcitonin and the bisphosphonate etidronate is more effective than either alone [27].

Adrenal Dysfunction

The adrenal glands consist of an outer layer (the cortex) and an inner core (the medulla) and play a major role in many endocrine and metabolic activities of the body. The adrenal cortex secretes three main groups of steroid hormones: glucocorticoids, mineralocorticoids, and sex hormones. Glucocorticoid secretion is under pituitary control. The mineralocorticoids are part of the renin-angiotensin system. Control of sex hormone production is not well understood. The adrenal medulla secretes catecholamines (epinephrine, norepinephrine) and is linked to the CNS by the autonomic nervous system.

Adrenocortical Insufficiency

Adrenal insufficiency occurs due to a disruption in the hypothalamic-pituitary-adrenal axis. Adrenal hypofunction may be a primary disorder (Addison disease) or secondary to adrenal insufficiency associated with hypopituitarism or adrenal function suppression by long-term exogenous glucocorticoids. The most common cause of Addison disease is idiopathic autoimmune adrenalitis [28]. Other pathological causes include tuberculosis, amyloidosis, and neoplasia. Adrenal insufficiency may also be congenital or familial.

Clinical Presentation

Chronic onset is very typical of Addison disease. Malaise, fatigue, weakness, and orthostatic hypotension are early symptoms and signs. Hyperpigmentation is also common with early disease; pale skin is typical of hypopituitarism. Late findings include anorexia, nausea, vomiting, diarrhea, hyponatremia, hyperkalemia, and fasting hypoglycemia. Patients may seek medical attention only in an adrenal crisis following some physical stress because early disease may go unrecognized. An adrenal crisis is characterized by muscle weakness, severe abdominal pain, and hypotension followed by shock, renal failure, and death. Since Addison disease is uncommon, affecting only about 1 in 20,000 in the United States and Western Europe, a high clinical suspicion is necessary to prevent the misdiagnosis of an adrenal crisis [29].

Diagnosis

The presence of hyponatremia, hyperkalemia, and a low 8:00 AM serum cortisol level would suggest a diagnosis of adrenal insufficiency. Demonstrating the inability of the adrenal cortex to increase cortisol production during an ACTH stimulation test is key [30]. Synthetic ACTH 0.25 mg is administered intravenously, and serum cortisol levels are determined at baseline and at 30, 60, and 90 min. The peak value should be at least double and 10 μg/dl greater than the basal value, though there is some disagreement over the definition of a normal response. If the test is abnormal, simultaneous 8:00 AM cortisol and ACTH levels can help distinguish primary from secondary adrenal insufficiency. Addison disease diagnosis involves a combination of low serum cortisol levels and persistently elevated levels of ACTH.

Management

Addison disease is treated with glucocorticoid and mineralocorticoid hormone replacement therapy, but the latter is not required for the treatment of adrenal insufficiency secondary to hypopituitarism.

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Hydrocortisone is the drug of choice for treating cases of adrenal crisis or insufficiency because of its glucocorticoid and mineralocorticoid effects [31]. Glucocorticoids are administered if there is a suspicion of an adrenal crisis, which may also require fluid and electrolyte therapy and vasopressors. Traveling patients should carry glucocorticoids for self-administration (injection or per rectum), and they should always wear medical identification. Monitoring for concomitant autoimmune diseases is important; up to 50 % of patients develop another autoimmune disorder during their lifetime [28].

Adrenocorticoid Excess

The stigmata of adrenocorticoid excess (Cushing syndrome) commonly results from the long-term use of exogenous glucocorticoids. Occasionally, it may be caused by an ACTH-secreting pituitary adenoma (Cushing disease), a glucocorticoid-producing adrenal adenoma or carcinoma, or another ACTH-producing neoplasm (usually lung).

Clinical Presentation

Characteristically, affected patients demonstrate rounded "moon facies," truncal obesity with a prominent dorsal cervical fat pad ("buffalo hump"), hypertension, hirsutism, osteoporosis, glucose intolerance, hypokalemia, and psychiatric disturbances. Patients may complain of proximal muscle weakness, menstrual abnormalities, and sexual dysfunction.

Diagnosis

Confirmation of the clinical diagnosis of adrenocorticoid excess and determining the cause may require the performance of a variety of tests [32]. If there is a clinical suspicion of Cushing syndrome, a 24-h urine specimen for free cortisol assay or a rapid low-dose dexamethasone suppression test may be obtained. For the latter, the patient is instructed to take 1 mg of dexamethasone between 11:00 PM and midnight, and a serum cortisol level is obtained at 8:00 AM the next morning. A value ≤ 5 μg/dL is normal. Values ≥ 5 μg/dL require further evaluation with a 2-day dexamethasone suppression test [33].

Management

Therapy is directed at eliminating the source of the excessive glucocorticoids through medication change or surgery for a neoplasm if indicated. Recently developed agents inhibit ACTH secretion from corticotrope tumors or antagonize cortisol action for patients in whom surgery is not possible, for those who decline adrenalectomy, or for those in whom surgery has failed [34].

Hyperaldosteronism

Primary hyperaldosteronism, or Conn syndrome, is a rare condition caused by an aldosterone-secreting neoplasia or hyperplasia of the adrenal gland [35]. 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. Profound diuretic-induced hypokalemia in a patient with diastolic hypertension is suggestive of hyperaldosteronism. Other patients present with muscle weakness, transient paralysis, paresthesia, tetany, isolated diastolic hypertension, hypernatremia, and hypokalemia. The diagnosis is complicated and involves measuring plasma aldosterone and renin concentrations, conducting imaging studies, and sometimes administrating selective adrenal vein catheterization. The treatment of a unilateral adenoma is surgical. Bilateral adrenal hyperplasia is treated using mineralocorticoid antagonists (e.g., spironolactone). Eplerenone is derived from spironolactone and considered a selective mineralocorticoid receptor antagonist with limited cross-reactivity for the androgen and progesterone receptors, thus lacking

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many of the significant sexually related adverse effects known to be associated with the use of spironolactone.

Hypoglycemia

Hypoglycemia not associated with the treatment of diabetes mellitus is characterized by "Whipple's triad": (1) a low plasma glucose level, (2) symptoms of neuroglycopenia, and (3) relief of these symptoms by carbohydrate intake [36]. Hypoglycemia is defined as a measured plasma glucose concentration <70 mg/dL, and severe hypoglycemia is defined as a blood glucose concentration <50 mg/DL [37]. The symptoms of hypoglycemia are due to two main processes: an adrenergic response (which usually occurs first when serum glucose levels begin to fall) and CNS dysfunction (which usually occurs later at lower glucose levels). Adrenergic symptoms and signs include anxiety, hunger, a feeling of warmth, nausea, palpitations, tremulousness, pallor, and diaphoresis. Neuroglycopenic symptoms and signs include dizziness, diplopia, blurred vision, inability to concentrate, amnesia, confusion, behavior changes, seizures, and coma. Because many patients present with vague symptoms or with a self-diagnosis of hypoglycemia, an important first step is to determine if there is a relation between the relief of hypoglycemia symptoms by carbohydrate intake and the corresponding plasma glucose levels [38].

Diagnosis

Ideally, a plasma blood glucose value is obtained at the time the patient has symptoms, but many times it is not practical. Some patients can be taught how to measure blood glucose levels at home and are asked to keep a diary of symptoms, blood glucose levels, and responses to carbohydrate ingestion. A hypoglycemic disorder is suspected if the patient exhibits Whipple's triad. Patients who have vague symptoms after meals not associated with hypoglycemia are said to have "idiopathic postprandial syndrome." The supervised 72-h fast is the classic diagnostic test for a hypoglycemic disorder; the 5-h glucose tolerance test is not considered to have diagnostic value [36]. During the 72-h fast, the patient is allowed only calorie-free and caffeine-free beverages. All medications are stopped. Levels of plasma glucose, insulin, C peptide, and proinsulin are determined every 6 h until the plasma glucose is 60 mg/dL or lower and then every 1–2 h. The test is ended when hypoglycemic plasma values are noted and the patient has symptoms of hypoglycemia. The absence of typical signs or symptoms precludes the diagnosis of a hypoglycemic disorder. A low plasma glucose level alone is not a sufficient finding for this diagnosis.

Management

Treatment is directed at the underlying cause. Patients who have undergone surgical procedures including gastrectomy, gastrojejunostomy, vagotomy, pyloroplasty are more prone to this condition secondary to enhanced transit of glucose into the intestine, which promotes insulin response. Sometimes, an explanation of the cause and advice to have frequent meals are all that is required. Individuals who exercise intensely may need to "carbohydrate-load" the day before and ingest carbohydrates during exercise. Medications may need to be discontinued or be given in a lower dose. The most commonly reported drugs associated with hypoglycemia are quinolones, pentamidine, quinine, beta blockers, and angiotensin-converting enzyme inhibitors and insulin-like growth factor (IGF); however, the evidence to support this association is of low quality [39]. Patients who have an alcohol use disorder may require specific treatment. Those with factitious hypoglycemia require psychiatric help. Patients with insulinomas are rare (about per million person-years) and may require localization with medical imaging prior to surgical treatment.

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Gout

Gout is a common cause of inflammatory arthritis [40]. Hyperuricemia is a common finding but does not inevitably cause disease. Hypertension, obesity, high alcohol intake, and the use of thiazides and loop diuretics contribute in an additive manner to the risk of gout.

Clinical Presentation

The clinical manifestations of gout are caused by the deposition of monosodium urate crystals in joints, bursae, and soft tissues. Acute gout presents as a self-limited episode of synovitis referred to as a "gout flare." Podagra usually refers to an acute gout attack in the feet, especially a gout flare of the great toe. Acute gout attacks can be debilitating and are the major component of the reported decreased health-related quality of life and decreased work productivity in patients with gout. Classic signs of chronic gout include tophi, deposits of uric acid in periarticular fibrous tissue, the cartilage of the external ear, and the kidneys.

Diagnosis

The diagnosis requires the direct identification of urate crystals in synovial fluid. Serum urate levels are typically normal during episodes of acute gout. An infectious cause may need to be excluded. The diagnosis of gout should prompt a search for associated medical conditions: alcoholism, various nephropathies, myeloproliferative disorders, and hypertension. Gout is also associated with insulin resistance. Certain hereditary disorders of purine metabolism such as hypoxanthine guanine phosphoribosyltransferase deficiency are also worth considering, especially when gout presents in the second or third decade of life.

Management

Options for the management of acute gouty arthritis include nonsteroidal anti-inflammatory drugs (NSAIDs), systemic or intra-articular corticosteroids, and oral colchicine. For best results, treatment needs to be initiated within 24 h of the onset of a gout flare. Established pharmacological urate-lowering therapy should be continued without interruption during an acute attack of gout. Prophylactic therapy is recommended for patients with three or more acute episodes per year with tophaceous deposits, with overproduction of uric acid, or who are on continued cyclosporine therapy. The American College of Rheumatology (ACR) guidelines on managing gout recommend allopurinol or febuxostat as first-line pharmacological urate-lowering therapy with a goal of reducing sUA to <6 mg/dL [41]. Probenecid is an alternative if contraindications exist or if the patient is intolerant to allopurinol and febuxostat. Anti-inflammatory prophylaxis with colchicine or NSAIDs is recommended upon initiation of urate-lowering therapy prophylaxis for acute gout attacks; corticosteroids are a second-line option. Intravenous pegloticase decreases serum uric acid and gout attacks and improves quality of life for those with chronic gout that is refractory to usual treatments. The key principles of nutrition therapy include a restriction of high purine meat, limiting alcohol intake, and reaching the proper body weight. Proponents of alternative therapies advocate a "Mediterranean diet," the intake of low-fat dairy products, and the use of cherry and related extracts [42].

Family and Community Issues

Endocrine and metabolic disorders may be associated with life-threatening crisis. For example, a patient with adrenal insufficiency (Addison's disease) who requires emergency surgery for multiple injuries

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sustained in a motor vehicle accident will need glucocorticoid and mineralocorticoid replacement therapy. The patient and family members need to be educated about the nature of these illnesses in the event of a medical emergency. Patients should be encouraged to wear medical alert identification as appropriate.

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Family Medicine
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Anemia

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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. Recent data from large samples selected to represent the population of the USA suggests that the lower limit of normal hemoglobin concentrations be 13.7 g/dL in young white men (ages 20–59 years) and 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.

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 [2]. 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 [3]. 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 [4]. 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 [4, 5]. 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

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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 [6]. 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. 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 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, especially of ice, suggests iron deficiency. 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. The stool should be examined for blood. Proprioception and balance deficits may occur in vitamin B12 deficiency.

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 [7]. Recent data 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 [8].

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Table 1 Classification of anemia based on MCV

Microcytic	**Macrocytic**
Iron deficiency	Non-megaloblastic
Thalassemia	Alcoholism
Anemia of chronic disease[a]	Chronic liver disease
Hemoglobin E[a]	Bone marrow disorders
Sideroblastic anemia[a]	Hypothyroidism[a]
Lead poisoning[a]	Sideroblastic anemias[a]
Hereditary[a]	Marked reticulocytosis
Myelodysplastic syndrome[a]	Spurious[a]
Severe alcoholism[a]	Normal variant[a]
Medications[a]	Neonatal period
Normocytic	Megaloblastic
Elevated reticulocyte count	Folate deficiency
Acute blood loss	Poor intake
Hemolysis	Malabsorption
Decreased reticulocyte count	Ethanol
Anemia of chronic disease	Medications
Chronic kidney disease	Pregnancy
Chronic liver failure	Infancy
Endocrine disease	High folate requirement
Iron deficiency	B12 (cobalamin) deficiency
Myelodysplastic syndromes	Pernicious anemia
Aplastic anemia[a]	Gastric or ileal surgery[a]
Pure red cell aplasia[a]	Ileal disease[a]
Myelophthisic anemia[a]	Strict veganism[a]
Sideroblastic anemia[a]	Fish tapeworm infection[a]
	Bacterial overgrowth[a]
	Pancreatic insufficiency[a]
	Medications[a]
	Congenital disorders[a]
	Medications (anticonvulsants, chemotherapy, zidovudine)

[a]Less common

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 [8].

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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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:

$$\text{correted reticulocyte } \% = \text{reticulocyte } \% \times \text{patient's Hct/normal Hct.}$$

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 and 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 teardrop 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. Current research focuses on other RBC indices such as MCH, reticulocyte cell Hgb content, and reticulocyte maturity index and the role of genetics in diagnosing anemia [8]. Algorithms for evaluation of microcytic, normocytic, and macrocytic anemias are provided in Figs. 1, 2, and 3.

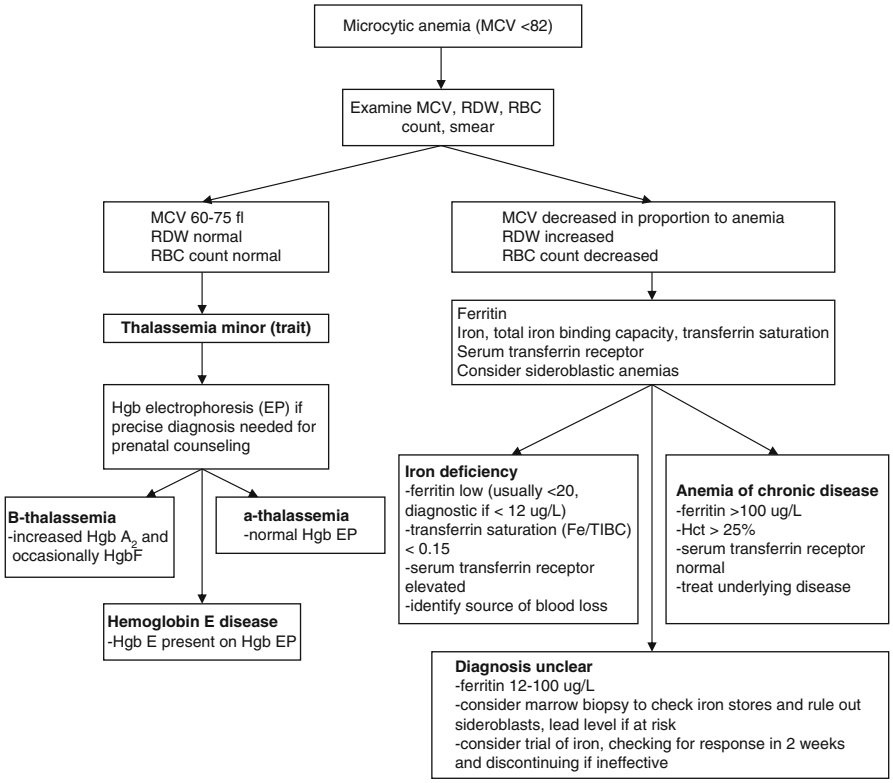

Fig. 1 Evaluation of microcytic anemia

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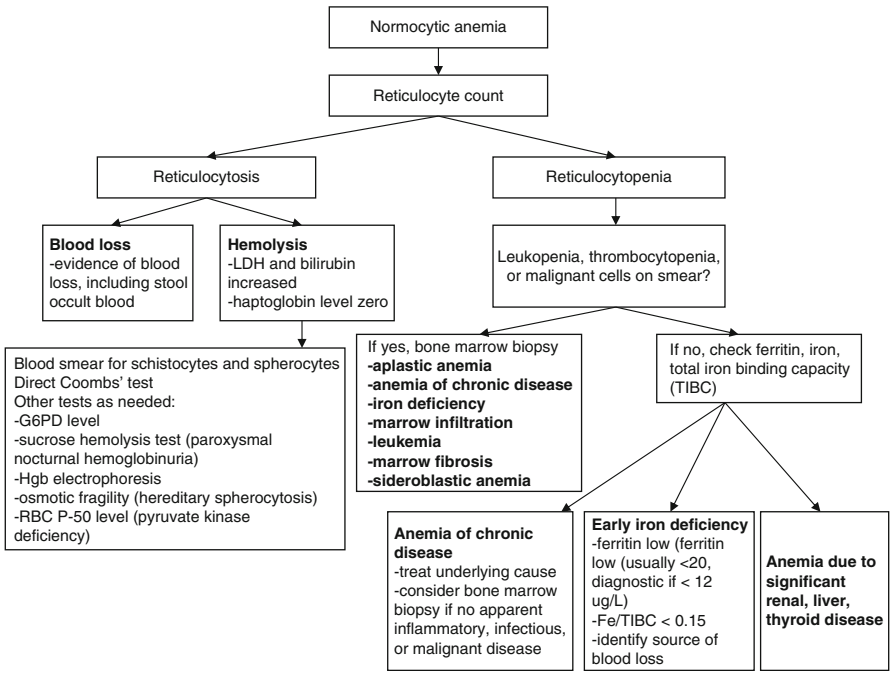

Fig. 2 Evaluation of normocytic anemia

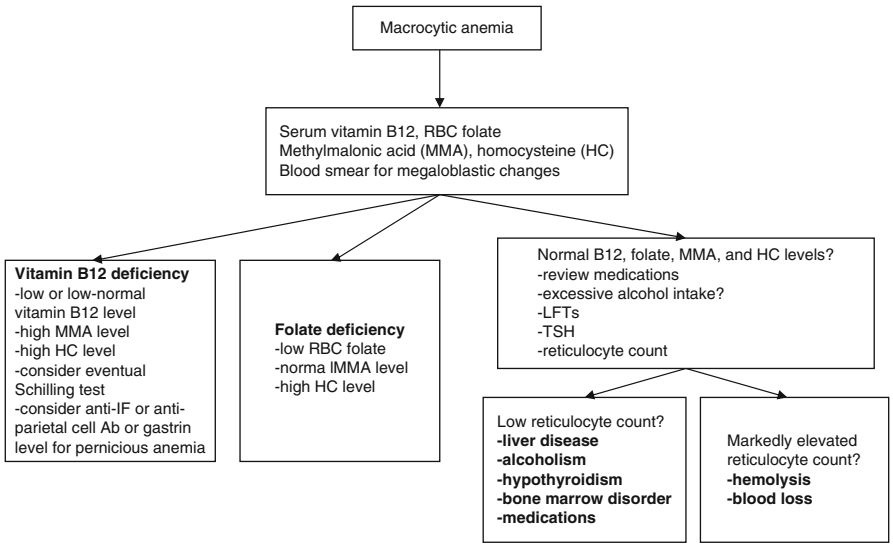

Fig. 3 Evaluation of macrocytic anemia

Microcytic Anemias

Iron Deficiency Anemia

IDA is probably the most common cause of anemia in the USA (Fig. 1). The recommended dietary allowance (RDA) for iron is 8 mg daily for men and 18 mg daily for women [9]. 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.

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In the USA, IDA accounts for approximately 40 % of anemia in children. 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 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 with 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 [10]. A serum ferritin and C-reactive protein level (CRP) should be checked. Elevations of both ferritin and CRP can occur in the setting of inflammation. On the other hand, a low serum ferritin (<10 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 [10].

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 malabsorption resulting from the surgery itself [11]. IDA is also seen in decreased absorption states such as celiac disease and gastrectomy.

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 1/3 of patients with IDA, no source of blood loss will be found despite this evaluation [12]. In these patients, prognosis is good, with anemia resolving in more than 2/3 without recurrence [13]. 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 [14].

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 [15]. 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 TfR may also be seen in increased or ineffective erythropoiesis [16, 17]. The transferrin

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receptor-ferritin index (ratio of sTfR 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 [17].

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 [18]. 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 [6]. 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 % [19]. Taking iron with vitamin C may help increase absorption [20]. Liquid iron preparations may be tried. Despite these measures, 10–20 % of patients will not tolerate oral iron replacement [21]. 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 RDW is usually normal, and the RBC count is normal or increased by

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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 (e.g., for prenatal counseling), 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

The absolute reticulocyte count or corrected reticulocyte percentage is important in determining the cause of a normocytic anemia (Fig. 2).

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.

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Table 2 Causes of hemolysis

Intrinsic (defect in RBCs)	Extrinsic (defect external to RBCs)
Hemoglobinopathies	Immune
Sickle syndromes	Autoimmune
Unstable hemoglobins	Lymphoproliferative
Methemoglobinemia	Malignancy
Membrane disorders	Collagen vascular disorders
Paroxysmal nocturnal hemoglobinuria	Drug induced (methyldopa, procainamide, quinidine, levodopa, sulfas, penicillin, NSAIDS)
Hereditary spherocytosis	Mechanical
Elliptocytosis	Disseminated intravascular coagulation (DIC)
Pyropoikilocytosis	Thrombotic thrombocytopenia purpura (TTP)
Stomatocytosis	Hemolytic uremic syndrome (HUS)
Enzyme deficiencies	Prosthetic heart valves
Glucose-6-phosphate dehydrogenase (G-6-PD)	Disseminated neoplasms
Pyruvate kinase	Burns
Glucose phosphate isomerase	Malignant hypertension
Congenital erythropoietic porphyria	Vasculitis
	Severe hypophosphatemia
	Physical activity (“march” hemoglobinuria)
	Strenuous exercise
	Hypersplenism
	Infections
	Clostridium, *Plasmodium*, *Borrelia*, *Mycoplasma*, *Babesia*, *Hemophilus*, *Bartonella*
	Bites
	Snakes
	Spiders

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 [22]. 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 [23]. 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 [15].

Treatment of ACD is directed toward the 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

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search for a coexisting cause. For example, a patient with rheumatoid 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 National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) recommends considering iron repletion in patients with CKD with anemia and serum transferrin saturation <30 % and ferritin <500 μg/L [24].

Therapy consists of ameliorating the renal disease and administering erythropoiesis-stimulating agents (ESAs), namely, erythropoietin and darbepoetin. ESA should be considered for all 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 [24]. 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. 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 USA, 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-vs.-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 acute polyarthropathy

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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 (MDSs) 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 [2]. Bone marrow biopsy is diagnostic, revealing characteristic dysplastic blood precursor cells. Treatment is largely supportive.

Macrocytic Anemias

Macrocytic anemias may be separated into megaloblastic and non-megaloblastic types, based on peripheral smear findings (Table 1) (Fig. 3). 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 [25].

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, and tapeworm infection.

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 is absent in 28 % of patients with neurologic abnormalities due to B12 deficiency [26].

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

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in 98 % of cases of clinically defined B12 deficiency. Falsely elevated levels occur in 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 is less specific, occurring in folate deficiency and kidney disease as well [27–29]. 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 [29]. 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 [30]. 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, or anticonvulsants, such as phenobarbital and phenytoin. 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, postsplenectomy, 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 [31].

Summary

Discovery of anemia should lead the physician to investigate the underlying cause of anemia. 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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Bleeding Disorders

Primary care physicians are often faced with bleeding disorders in several situations. They may be faced with diagnosing a previously unknown bleeding disorder (in both adults and children) but also might be managing or comanaging a patient with a chronic bleeding disorder.

Diagnosis and Evaluation

Adult and pediatric patients with bleeding disorders can present in many ways: many have the complaint of easy bruising (although this is usually not pathologic), excessive bleeding from menses, or postsurgical bleeding. A complete history is the most critical part of the examination and focuses on the "bleeding score" – a risk assessment specifically designed to evaluate for risk of von Willebrand's disease but may be useful in ascertaining risk and severity of many bleeding disorders. See Table 1. Further, questions regarding family history are essential: A positive family history in first-degree relatives (especially regarding menorrhagia) is reason alone to justify a workup. A dietary history can be useful in identifying patients at risk for vitamin K deficiency. Finally, ensure that a full medical reconciliation is completed, as several medications may cause easy bleeding. See Tables 1 and 2 [1].

If the history warrants a further workup, blood work should be done. A PT/PTT, bleeding time versus platelet function assay (preferred), and a mixing study should be used to aid diagnosis. See Table 3 for common patterns of laboratory studies for bleeding diagnoses. It is important to mention that even if the lab workup is normal – if there is enough clinical concern (i.e., high bleeding score) – the patient should be referred to a hematologist for further workup.

Management of Bleeding Disorders

Primary care management of bleeding disorders should be based on comfort level of both the patient and the physician. Due to the significant cost and complexity of management, many primary care physicians refer at diagnosis. However, a patient-centered approach is necessary to deal with the psychosocial disorders associated with bleeding disorders (see Table 4). Referral to an appropriate support group or a family counselor may improve the patient's and family's level of functioning and compliance.

Congenital Bleeding Disorders

Von Willebrand's Disease

Von Willebrand's disease (vWD) is the most common congenital bleeding disorder. The prevalence of vWD may be as high as 1.5 % of the population; the most severe form has a prevalence rate of 1 in 1 million. vWD is an inherited hemorrhagic disorder characterized by deficiency of von Willebrand factor (vWF). vWF is necessary for normal interaction of platelets with vessel walls. vWD is inherited in an autosomal dominant pattern, with males and females equally affected. There are four types and multiple subtypes of vWD. Many patients with vWD also have low levels of factor VIII [3].

Hemorrhage with vWD is highly variable. Epistaxis, gastrointestinal bleeding, easy bruising, and menorrhagia are characteristic of vWD. Hemarthroses are rare. Bleeding following trauma, dental extractions, or operations may be severe. Patients with vWD types I and II platelet type usually have mild or no bleeding problems. Patients with type III disease have severe bleeding problems.

The diagnosis of vWD is confirmed by laboratory findings of prolonged bleeding time, decreased factor VIII levels, decreased vWF activity, and decreased vWF antigen. The PT, APTT, and platelet count are usually normal (Table 3).

The goals of therapy for vWD are to correct coagulation abnormalities, prevent hemorrhage, and return the levels of vWF and factor VIII to normal. For patients with mild vWD, DDAVP administered intranasally or intravenously at a dose of 0.2–0.3 μg/kg body weight can be

Table 1 Bleeding score

Source	Score					
	−1	0	1	2	3	4
Epistaxis	N/A	No/trivial	>5 episodes per year or lasts >10 min	Consultation to specialist but no intervention	Packing, cauterization, or antifibrinolytics	Blood transfusion, replacement therapy, or desmopressin
Cutaneous (bruises)	N/A	No/trivial	>1 cm and no trauma	Consultation to specialist but no intervention	N/A	N/A
Minor wounds	N/A	No/trivial	>5 episodes per year or lasts >5 min	Consultation to specialist but no intervention	Surgical hemostasis	Blood transfusion, replacement therapy, or desmopressin
Oral cavity	N/A	No	Bleeding noted once	Consultation to specialist but no intervention	Surgical hemostasis or antifibrinolytics	Blood transfusion, replacement therapy, or desmopressin
Gastrointestinal	N/A	No	Associated with angiodysplasia, hemorrhoids, portal hypertension, ulcer	Spontaneous	Surgical hemostasis, blood transfusion, replacement therapy, desmopressin, or antifibrinolytics	N/A
Tooth extraction	No bleeding in two extractions	None performed, or no bleeding in one extraction	Bleeding noted in <25 % of all procedures	Bleeding noted in >25 % of all procedures	Resuturing/packing	Blood transfusion, replacement therapy, or desmopressin
Surgery	No bleeding in two surgeries	None performed or no bleeding in one surgery	Bleeding noted in <25 % of all procedures	Bleeding noted in <25 % of all procedures	Surgical hemostasis or antifibrinolytics	Blood transfusion, replacement therapy, or desmopressin

(*continued*)

Table 1 (continued)

Source	Score					
Menorrhagia	N/A	No	Consultation to specialist but no intervention	Antifibrinolytics, pill use	Dilatation and curettage, iron therapy	Blood transfusion, replacement therapy, or desmopressin
Postpartum hemorrhage	No bleeding in two deliveries	None performed or no bleeding in one delivery	Consultation to specialist but no intervention	Dilatation and curettage, iron therapy, antifibrinolytics	Blood transfusion, replacement therapy, or desmopressin	Hysterectomy
Muscle hematomas	N/A	Never	Post-trauma, no therapy	Spontaneous, no therapy	Spontaneous or traumatic, requiring desmopressin or replacement therapy	Spontaneous or traumatic, requiring surgery or blood transfusion
Hemarthrosis	N/A	Never	Post-trauma, no therapy	Spontaneous, no therapy	Spontaneous or traumatic, requiring desmopressin or replacement therapy	Spontaneous or traumatic, requiring surgery or blood transfusion
Central nervous system	N/A	Never	N/A	N/A	Subdural	Intracerebral

A score >4 has a sensitivity of 100 % and a specificity of 87 % for von Willebrand's disease [2]

effective [4]. Oral contraceptives can increase plasma levels of factor VIII and vWF and are useful for women with vWD whose primary problem is menstrual bleeding. Intravenous factor VIII is used to treat patients with more severe bleeding problems. Treatment is titrated to the clinical status of the patient. Surgical and dental procedures can be safely performed in most patients with vWD. Treatment is started (DDAVP or factor VIII) 1 h prior to the procedure and is continued for 2–3 days after the procedure. The goal of perioperative therapy is to keep the bleeding time within the normal range. vWD is preventable only through genetic counseling. It is passed via an autosomal dominant pattern, with 50 % of the children of a parent with vWD at risk to inherit the disease. vWD can be detected in utero via chromosomal analysis. The family and community issues are similar to concerns faced by patients with hemophilia A.

Table 2 Medications that cause bleeding and bruising [1]

Common	Rare
Aspirin	Cephalosporins
Clopidogrel (Plavix)	Ginkgo biloba
Heparin	Gold
Nonsteroidal anti-inflammatory drugs	Interferon
Warfarin (Coumadin)	Metaxalone (Skelaxin)
Other anticoagulants	Penicillins
	Propylthiouracil
	Selective serotonin reuptake inhibitors
	Testosterone replacement
	Tricyclic antidepressants

Hemophilia A

Hemophilia A is an autosomal X-linked recessive deficiency of factor VIII. Because of the mode of transmission and gene expression, males have hemophilia A, and females are usually asymptomatic carriers of the hemophilia A gene. All daughters of a hemophiliac father are carriers of the hemophilia A gene; all his sons are normal. The children of a female hemophilia A carrier have a 50 % chance of being affected by the gene. Hemophilia A affects approximately 1 in 10,000 to 1 in 20,000 males in the United States [5]. Most children with severe hemophilia present within the first year of life due to easy bruising, hemarthrosis, oral bleeding, and post-procedure bleeding.

Hemophilia A usually presents with hemorrhage into a joint or a muscle. Excessive bleeding following minor cuts or abrasions is rare because of normally functioning platelets and normal vessel walls. A common first presentation is either a hemarthrosis or large bruise following a fall during the first 2 years of life or prolonged bleeding following neonatal circumcision. The most common bleeding sites are the joints (knees, elbows, ankles, shoulder, hips, wrists), muscles, renal tract, nervous system, gastrointestinal tract, and oral cavity following tooth extraction.

Screening coagulation tests reveal a normal platelet count, normal bleeding time, normal prothrombin time (PT), and prolonged activated partial thromboplastin time (APTT) (Table 3). The diagnosis is confirmed by obtaining a serum factor VIII assay (normal 1.0 U/mL). The disease is classified as mild, moderate, or severe depending on the serum level of factor VIII activity [3].

Table 3 Laboratory abnormalities seen with bleeding disorders

Disease	Platelet count	Bleeding time	PT	APTT
Hemophilia A and B	Normal	Normal	Normal	Prolonged
von Willebrand's disease	Normal	Prolonged	Normal	Normal
Thrombocytopenia	Low	Prolonged	Normal	Normal
Vitamin K deficiency	Normal	Normal	Prolonged	Normal or prolonged

PT prothrombin time, *APTT* activated partial thromboplastin time
Normal values, platelet count 250,000–500,000/mm^3; bleeding time, Ivy 2–7 min, Duke 1–4 min; APTT 34–54 s; PT 10–14 s

Table 4 Common psychosocial concerns associated with hemophilia (and other bleeding disorders) [1]

Responses of the patient and family to a chronic illness, including overprotection
"Daredevil syndrome" – patient taking risks above those expected for the developmental stage
School and vocational problems
Financial burdens (treatment cost $10,000–$50,000/year)
Concern about infections from blood products (human immunodeficiency virus (HIV) infection prior to 1985, hepatitis B and C)
Peer and sibling relationship problems

Hemorrhage in hemophilia is prevented by intravenous infusion of recombinant factor VIII or human-derived factor VIII concentrates (treated to inactivate or remove viruses). The plasma factor VIII level is maintained at 0.3 U/mL if the patient experiences minor hemorrhage, 0.5 U/mL with severe hemorrhage, and 0.8–1.0 U/mL with life-threatening hemorrhage. Intravenous desamino-γ-D-arginine vasopressin (DDAVP) (desmopressin acetate 0.3 μg/kg) is the treatment of choice for the patient with mild hemophilia; the mechanism of action is unclear [6]. Complications of bleeding are managed conservatively or by drainage depending on the site and severity.

Surgical and dental procedures can be performed for the patient with hemophilia A. The following factors should be considered:

1. The procedure should be done in a facility with an adequate blood bank and surgeons and dentists experienced in treating patients with hemophilia A.
2. No intramuscular medications are prescribed, and no salicylate is given.
3. The factor VIII level should be maintained at 80–100 % of normal (0.8–1.0 U/mL).
4. ∈-Aminocaproic acid (EACA) (4 g PO q4–6 h for 2–8 days) can be used as single or adjunctive postoperative therapy for dental procedures [4]. ∈-Aminocaproic acid is a potent inhibitor of fibrinolysis (inhibits plasminogen activation) and enhances hemostasis in hemophiliacs. Hemophilia A is preventable only via genetic counseling (see chapter "▶ Genetic Disorders"). A family genogram is invaluable for tracking the illness across generations. Women who are at risk for being carriers for hemophilia A can be identified as normal or carriers through factor VIII antibody studies and DNA analysis, with a detection rate of 70–100 % [7]. Hemophilia A can usually be detected in a male fetus using chromosome studies when there is a family history of hemophilia A (i.e., the mother is at risk of being a carrier). Detection of de novo cases, with no family history, is difficult.

Hemophilia B

Hemophilia B is an X-linked recessive factor IX deficiency. It has an incidence of approximately 1 in 30,000 males and is diagnosed by factor IX assay. Hemophilia B is clinically indistinguishable from hemophilia A. Treatment of hemophilia B is intravenous recombinant or human-derived factor IX concentrate. DDAVP has no value in hemophilia B. However, treatment with fibrinolytic inhibitors (i.e., EACA) is indicated [8].

Easy Bruising

Simple, easy bruising (devil's pinches) is an ill-defined condition that presents with bruises on the lower extremities and trunk [9]. In one survey of 500 people, 18 % of healthy individuals reported easy bruising, with women predominant [10]. It may be considered as the underlying etiology only when all other life-threatening causes have been ruled out.

Senile purpura is a characteristic lesion of the elderly [11]. The lesion is caused by progressive loss of collagen in vessels and skin, possibly hastened by ultraviolet (sun) exposure. The lesions of senile purpura usually occur on the upper extremities, especially the back of the hands, wrists, and forearms. The lesions are large, dark, and well demarcated. The diagnosis

is made clinically. Screening coagulation studies are usually normal. There is no specific treatment. Most lesions of senile purpura resolve slowly. Counseling the patient regarding the benign nature of the illness is recommended. Minimizing sun exposure may slow some of the skin changes of aging.

Acquired Bleeding Disorders

Vitamin K Deficiency

Vitamin K is a fat-soluble compound essential to the synthesis of factors II, VII, IX, and X. The sources of vitamin K are dietary (especially green, leafy vegetables) and synthesis of vitamin K by intestinal bacteria. The daily adult requirement of vitamin K is 100–200 μg/day. Deficiency states of vitamin K can be seen in the newborn (hemorrhagic disease), the elderly, and patients with liver disease, after ingestion of vitamin K antagonists (i.e., warfarin), or with long-term antibiotic use (elimination of gastrointestinal flora).

Vitamin K deficiency presents with bleeding in the skin or from mucosal surfaces. Internal bleeding and hemarthroses are rare. The PT is prolonged, the bleeding time and platelet count are usually normal, and the APTT may be prolonged (Table 3).

Vitamin K deficiency is diagnosed by correcting clinical and laboratory abnormalities with vitamin K replacement. A direct laboratory assay for vitamin K is also available [12].

In the case of life-threatening hemorrhage, fresh frozen plasma is given intravenously to return the PT to normal and stop the bleeding. In less urgent situations, vitamin K can be given by the intramuscular, intravenous, or oral route (AquaMEPHYTON 10–15 mg). The goal of therapy is to prevent further bleeding and to return the PT to normal. Treatment with vitamin K usually corrects the PT within 24–48 h.

A diet with adequate amounts of vitamin K-containing foods (especially green, leafy vegetables), avoidance of hepatotoxic agents, and judicious use of long-term antibiotics can prevent vitamin K deficiency. Vitamin K 0.5–1 mg IM should be given to all newborns to prevent hemorrhagic disease of the newborn [13]. Vitamin K supplementation is also recommended during pregnancy for women on anticonvulsant therapy or prolonged treatment with certain antibiotics [14]. Vitamin K deficiency may be a sign of neglect in the elderly patient, whose diet may be deficient.

Thrombocytopenia

Reduction in platelet counts may not always be clinically apparent (manifesting in easy bruising/bleeding) and is often noted incidentally on routine lab work – especially in routine hospital work. Platelets play a crucial role in hemostasis through adhesion, "platelet plug" formation, and release of substances that promote platelet aggregation. Bleeding due to platelet disorders is usually in the skin or from mucosal surfaces. Thrombocytopenia is defined as a platelet count below 100,000/mm^3. Atraumatic bleeding usually is not a problem with a platelet count above 20,000/mm^3. Traumatic bleeding can occur with platelet counts of 40,000–60,000/mm^3. Other routine clotting studies are usually normal except for a prolonged bleeding time.

Diagnosis of thrombocytopenia has a prognostic significance. In one study of 217 persons with platelet counts from 100 to 150 × 10 per μL over a 10-year period, 64 % of patients' platelet counts normalized or remained stable. The probability of developing immune thrombocytopenic purpura or an autoimmune disorder was approximately 7 %. Four cases of myelodysplastic syndrome were diagnosed (2 %), all of which were in older patients [15].

Most surgical and invasive procedures can be performed safely in patients with platelet counts greater than 50 × 10 per μL. Other procedures, such as bone marrow biopsy, bronchoscopy, and endoscopy, can be completed safely in patients with platelet counts greater than 20 × 10 per μL

provided that no other bleeding abnormalities are noted [15].

Diagnosis of Thrombocytopenic Disorders

Thrombocytopenia can result from several mechanisms: decreased platelet production, increased platelet consumption, or sequestration (see Table 5 for etiologies). A systematic approach should be used to evaluate incidental thrombocytopenia. During the patient history, physicians should inquire about easy bruising/petechiae, melena, rashes, fevers, and bleeding. They also should inquire about medication use, immunizations, recent travel, transfusion history, family history, and medical history. A history of acute and chronic alcohol use should be obtained. Any recent hospitalization or heparin exposure should raise the possibility of heparin-induced thrombocytopenia. Pregnant patients with visual symptoms, headaches, abdominal pain, or influenza-like symptoms may have preeclampsia or HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome. The physical examination should include the eyes (e.g., hemorrhage is suggestive of central nervous system bleeding), abdomen (e.g., splenomegaly, hepatomegaly), lymph nodes (e.g., lymphadenopathy), skin (e.g., petechiae, purpura, bruising), and neurologic system. Bleeding (e.g., epistaxis, mucosal,

Table 5 Etiologies of thrombocytopenia [1]

Decreased production	Increased platelet consumption	Sequestration
Bone marrow failure (e.g., aplastic anemia, paroxysmal nocturnal hemoglobinuria, Shwachman-Diamond syndrome)	Alloimmune destruction (e.g., posttransfusion, neonatal, posttransplantation)	Chronic alcohol abuse[a]
Bone marrow suppression (e.g., from medication, chemotherapy, or irradiation)	Autoimmune syndromes (e.g., antiphospholipid syndrome, systemic lupus erythematosus, sarcoidosis)	Dilutional thrombocytopenia (e.g., hemorrhage, excessive crystalloid infusion)
Chronic alcohol abuse[a]	Disseminated intravascular coagulation[a]/severe sepsis[a]	Gestational thrombocytopenia
Congenital macrothrombocytopenias (e.g., Alport syndrome, Bernard-Soulier syndrome, Fanconi anemia, platelet-type or pseudo-von Willebrand's disease, Wiskott-Aldrich syndrome)	Drug-induced thrombocytopenia	Hypersplenism (e.g., distributional thrombocytopenia)
Infection[b] (e.g., cytomegalovirus, Epstein-Barr virus, hepatitis C virus, HIV, mumps, parvovirus B19, rickettsia, rubella, varicella zoster virus)	Heparin-induced thrombocytopenia	Liver disease (e.g., cirrhosis, fibrosis, portal hypertension)
Myelodysplastic syndrome	Immune thrombocytopenic purpura[a]	Pseudothrombocytopenia
Neoplastic marrow infiltration	Infection[b] (e.g., cytomegalovirus, Epstein-Barr virus, hepatitis C virus, HIV, mumps, parvovirus B19, rickettsia, rubella, varicella zoster virus)	Pulmonary emboli
Nutritional deficiencies (vitamin B and folate)	Mechanical destruction (e.g., aortic valve, mechanical valve, extracorporeal bypass)	Pulmonary hypertension
	Preeclampsia/HELLP syndrome	
	Thrombotic thrombocytopenic purpura/ hemolytic uremic syndrome	

HELLP hemolysis, elevated liver enzymes, and low platelet count, *HIV* human immunodeficiency virus
[a]More than one mechanism of action
[b]Thrombocytopenia with infection is usually caused by bone marrow suppression. In some cases, the thrombocytopenia is also immune mediated

Table 6 Clinical considerations to assist with diagnosis of thrombocytopenia [16]

Clinical consideration	Possible diagnosis
Timing	
Acute	Acute infection (primarily viral), acute leukemias, aplastic anemia, chemotherapy or irradiation, drug-induced thrombocytopenia, HELLP syndrome/preeclampsia, heparin-induced thrombocytopenia, ITP, malignancies with marrow infiltration, myelofibrosis, TTP/HUS
Chronic	Chronic alcohol abuse, congenital syndromes, ITP, liver disease, myelodysplastic syndrome
History	
Family history	Congenital thrombocytopenia
Liver disease	Chronic alcohol abuse, chronic liver disease
Pregnancy	Gestational thrombocytopenia, HELLP syndrome/preeclampsia
Recent change in medication	Drug-induced thrombocytopenia
Recent hospitalization	Heparin-induced thrombocytopenia
Recent immunization	MMR, varicella, influenza A (H_1N_1)
Recent transfusion or high-risk behavior	Alloimmune destruction, posttransfusion purpura, viral infection (HCV, HIV)
Recent travel	Dengue fever, malaria, rickettsial diseases
Recent valve replacement surgery	Mechanical destruction
Symptoms	
Abdominal pain	HELLP syndrome/preeclampsia, HUS, platelet sequestration
Recent fever	Viral infections (CMV, EBV, HIV, influenza A (H_1N_1), parvovirus B19), TTP, rickettsial diseases
Weight loss or night sweats	HIV, malignancies (acute leukemias, myelodysplastic syndrome)
Physical examination	
Acute rash	Rickettsial diseases, SLE, viral infections
Generalized lymphadenopathy	Viral infections (CMV, EBV, HIV), SLE, myeloproliferative disorders, lymphoproliferative disorders
Hepatomegaly	Chronic liver disease, acute leukemias, viral infections (CMV, EBV, HBV, HCV)
Neurologic	TTP
Splenomegaly[a]	Autoimmune (SLE, sarcoidosis), hypersplenism, viral infections

CMV cytomegalovirus, *EBV* Epstein-Barr virus, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *HELLP* hemolysis, elevated liver enzymes, and low platelet count, *HIV* human immunodeficiency virus, *HUS* hemolytic uremic syndrome, *ITP* immune thrombocytopenic purpura, *MMR* measles, mumps, and rubella, *SLE* systemic lupus erythematosus, *TTP* thrombotic thrombocytopenic purpura

[a]Ultrasonography may be useful in patients who are obese

gastrointestinal, genitourinary) also should be assessed. Results of the history and physical examination are summarized in Table 6: *Clinical considerations to assist with diagnosis of thrombocytopenia.* A peripheral smear should also be obtained in order to assist with diagnosis, as several findings may assist with diagnosing the underlying etiology.

Treatment is unnecessary in patients with mild thrombocytopenia and is reserved for the patient who is bleeding because of thrombocytopenia or whose platelet count is below 20,000/mm^3. The goal of therapy is to stop the bleeding and return the platelet count to more than 20,000/mm^3. Treatment is summarized in Table 7: *Treatment of thrombocytopenia.*

Emergent Thrombocytopenia

Idiopathic Thrombocytopenic Purpura

Idiopathic thrombocytopenic purpura (ITP) is caused by interaction of immunoglobulin G (IgG) and other antibodies with megakaryocytes

Table 7 Treatment of thrombocytopenia

Etiology	Severity	Clinical presentation	Evaluation	Treatment	Comments
Bone marrow suppression by irradiation, chemotherapy, or neoplasia	Moderate to severe	History of exposure, comorbid preexisting disease, or malignancy Acute leukemias present with fatigue, weakness, bruising, hepatosplenomegaly	Directed by preexisting diagnosis, specific cancer markers Abnormal blood smear or bone marrow biopsy	Based on underlying etiology	Usually affects all cell lines
Chronic alcohol abuse	Mild to moderate	Findings range from normal to evidence of cirrhosis or hepatic failure	Positive screening questionnaire, abnormal liver function tests (AST/ALT >2, GGT), macrocytosis, folate deficiency, hepatic imaging as clinically indicated	Cessation of alcohol use, vitamin and nutritional replacement	Cessation of alcohol use may lead to platelet rebound (>500 × 10 per μL [500 × 10 per L]) at 1–2 weeks
Chronic liver disease	Mild to severe	Symptoms are variable and based on evidence of cirrhosis, liver dysfunction, gastrointestinal bleeding, ascites, hepatomegaly, and jaundice	Abnormal intrinsic liver function testing, imaging, and liver biopsy as clinically indicated	Based on etiology, often supportive	Hypersplenism often is present contributing to thrombocytopenia
Congenital thrombocytopenia	Mild to moderate	Long history of abnormal platelet count or family history of thrombocytopenia	Many disorders associated with giant platelets, neutrophil inclusions, or other congenital anomalies	Varies depending on primary abnormality	Often asymptomatic when there is no bleeding diathesis
Disseminated intravascular coagulation	Severe	Acute illness; bleeding, acute renal failure, hepatic and respiratory dysfunction, and shock are common clinical manifestations Secondary to other comorbid conditions, such as sepsis, trauma, burns, or malignancy	Prolonged coagulation activation, elevated fibrin markers, and accelerated fibrinolysis (low fibrinogen levels)	Supportive treatment with platelet and clotting factor replacement therapy	Mortality rates exceed 20 %; prognosis is based on treating the underlying disorder
Drug-induced thrombocytopenia	Moderate to severe	Can range from asymptomatic to evidence of clinical bleeding	Detailed history of recent prescription medications, nutritional supplements, and over-the counter agents	Removal of offending agent Serial platelet monitoring until normalization	May be initially indistinguishable from ITP Often resolves within seven to 14 days after agent is discontinued

Heparin-induced thrombocytopenia	Moderate to severe	Thrombocytopenia or a 50 % reduction after exposure to heparin or low-molecular-weight heparin Arterial and venous thrombosis	History of heparin use, erythema or necrosis at site of injection, thrombosis, ELISA test for presence of platelet factor 4 antibodies	Immediate withdrawal of heparin, treatment with nonheparin anticoagulant	Warfarin (Coumadin) monotherapy may induce thrombosis and is contraindicated in the acute setting
Gestational thrombocytopenia	Mild	Asymptomatic with platelet counts rarely $<70 \times 10$ per μL (70×10 per L)	Identified during initial prenatal CBC No associated fetal thrombocytopenia Spontaneous resolution after delivery	No treatment indicated Platelet counts approaching 50×10 per μL (50×10 per L) often are considered ITP and treated with corticosteroids or IVIG	Possible immunologic etiology May be difficult to distinguish from ITP before delivery Up to 15 % of infants with thrombocytopenia are born to women with ITP
Immune thrombocytopenic purpura	Mild to moderate	Often asymptomatic, although symptoms can range from petechiae and easy bruising to severe bleeding diathesis (rare) Secondary ITP may present in patients with autoimmune disorders, infections (e.g., cytomegalovirus, Epstein-Barr virus, *Helicobacter pylori*, hepatitis C virus, human immunodeficiency virus, varicella zoster virus), and lymphoproliferative disorders	Remainder of CBC normal, normal peripheral blood smear, absence of clinically associated conditions Secondary ITP causes should be investigated as clinically indicated	Corticosteroids, IVIG, rituximab (Rituxan), splenectomy Treatment not indicated for platelet counts $> 50 \times 10$ per μL unless active bleeding Secondary ITP also requires treatment of underlying cause	Diagnosis of exclusion Patients older than 60 years should have bone marrow biopsy to rule out myelodysplastic syndrome or lymphoproliferative disorder MMR vaccination causes one case of ITP per 40,000 doses
Infections (viral or rickettsial)	Mild to moderate	Viral: prodrome or asymptomatic; known viruses include cytomegalovirus, Epstein-Barr virus, hepatitis B and C viruses, human immunodeficiency virus, parvovirus B19, varicella zoster virus Rickettsial: Lyme disease, Rocky Mountain spotted fever, ehrlichiosis; tick-borne illnesses present with fever, headache, malaise, arthralgias, and rash	Viral: diagnosis based on viral etiology, directed antiviral titer testing if available Rickettsial: ELISA testing may be useful	Viral: based on viral etiology; most self-limited viral infections are supportive Rickettsial: doxycycline is recommended in symptomatic tick-borne disease	Viral: varicella (live) and influenza A (H_1N_1) vaccinations have been reported to cause mild transient thrombocytopenia Rickettsial: ehrlichiosis causes more severe thrombocytopenia than Rocky Mountain spotted fever and Lyme disease

(*continued*)

Table 7 (continued)

Etiology	Severity	Clinical presentation	Evaluation	Treatment	Comments
Preeclampsia/HELLP syndrome	Mild to moderate	Elevated blood pressure, visual symptoms, headache, right upper quadrant abdominal pain, influenza-like symptoms	CBC, liver function test, urine protein level, increased uric acid level, increased LDH level, basic metabolic panel	Delivering the fetus; intravenous magnesium sulfate	Recovery usually is within 3 days of delivery. If persistent beyond the third day after delivery, presume thrombotic thrombocytopenic purpura
Pseudothrombocytopenia	Factitious	Asymptomatic; in vitro agglutination of platelets	Repeat CBC using non-EDTA anticoagulant	No treatment indicated	Peripheral blood smear will demonstrate clumping
Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome	Moderate to severe	Most common presentation is nonspecific and includes abdominal pain, nausea/vomiting, and weakness; patients with thrombotic thrombocytopenic purpura may have neurologic abnormalities at presentation	Microangiopathic hemolytic anemia, impaired renal function, neurologic abnormalities, proteinuria, increased LDH, increased bilirubin, and decreased haptoglobin levels	Plasma exchange	10–30 % mortality despite treatment; in children, hemolytic uremic syndrome presents with gastroenteritis (bloody diarrhea) and 60 % will have thrombocytopenia

ALT alanine transaminase, *AST* aspartate transaminase, *CBC* complete blood count, *EDTA* ethylenediaminetetraacetic acid, *ELISA* enzyme-linked immunosorbent assay, *GGT* γ-glutamyltransferase, *HELLP* hemolysis, elevated liver enzymes, and low platelet count, *ITP* immune thrombocytopenic purpura, *IVIG* intravenous immunoglobulin, *LDH* lactate dehydrogenase, *MMR* measles, mumps, and rubella

or platelets, resulting in increased platelet destruction. ITP can present as a primary problem or be associated with such condition as malignancies, collagen vascular disease, or viral illnesses. Acute ITP is most common in children, and chronic ITP is more common in adults, with a male/female ratio of 1:3 [16]. Acute ITP occurs most commonly between the ages of 2 and 9 years; chronic ITP occurs chiefly between the ages of 20 and 50 years.

Patients with ITP may be asymptomatic, or they may present with persistent skin bleeding (especially in areas exposed to trauma) or mucosal surface bleeding (i.e., epistaxis, menorrhagia, ecchymoses). Internal hemorrhage and hemarthroses are rare. Intracranial hemorrhage, though rare, can be a serious complication of ITP. There is no lab test for ITP. The diagnosis is purely clinical.

Thrombotic Thrombocytopenic Purpura

Thrombotic thrombocytopenic purpura (TTP) is primarily a disease of adults of largely unknown etiology. The hallmark of TTP is widespread platelet thrombi occurring throughout the microcirculation. Although rare, TTP can be fatal in up to 90 % of untreated patients.

The clinical manifestations of TTP may include hemorrhage, hemolytic anemia, neurologic problems (headache, mental status changes, seizures, coma, and focal neurologic changes), hematuria, renal failure, and fever.

The diagnosis of TTP is made based on the clinical findings and laboratory findings including severe thrombocytopenia, red cell fragmentation, reticulocytosis, elevated indirect serum bilirubin, decreased haptoglobin, and proteinuria. Disseminated intravascular coagulation is usually not associated with TTP. Severe TTP is treated with prednisone (1–2 mg/kg/day) and plasmapheresis.

The hemolytic uremic syndrome (HUS) is clinically similar to TTP [17]. HUS is usually seen in children following infections by viruses, *Escherichia coli*, or *Shigella* species. The clinical picture of HUS includes thrombocytopenia and hemolytic anemia. Neurologic symptoms are less common in HUS than in TTP. The treatment for patients with HUS is plasma exchange. Syndromes resembling TTP/HUS have been seen in patients receiving certain chemotherapeutic agents.

Disorders of the Vascular Wall

The integrity of the vascular wall is essential for maintenance of normal coagulation. Some causes of vascular wall disruption are listed in Table 8. Vascular causes of bleeding (purpura) tend to manifest most often on the lower extremities. Purpura of the head and neck is usually caused by fat emboli, amyloidosis, or mechanical

Table 8 Bleeding from vascular abnormalities

Congenital	Acquired
Hereditary hemorrhagic telangiectasia	*Mechanical*
Angiokeratoma corporis diffusum	Trauma
Ataxia telangiectasia	Increased venous pressure
Cavernous hemangioma	*Decreased supporting tissue*
Ehlers-Danlos syndrome	Senile purpura
Pseudoxanthoma elasticum	Scurvy
Osteogenesis imperfect	Corticosteroids
Marfan syndrome	Amyloidosis
	Chemical agents
	Warfarin (Coumadin)
	Snake venoms
	Infections: meningococcus, rickettsiae, streptococci, shigellae, gram-negative bacteria, measles, rubella, diphtheria
	Vasculitis: Henoch-Schönlein purpura
	Vascular obstruction
	DIC
	Fat emboli
	Leukostasis
	Paraproteinemia
	Proliferative retinopathy
	Idiopathic causes

stresses. Bleeding from vascular causes (with some exceptions) is usually confined to the skin.

Congenital Disorders

Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease) is a congenital disorder. Bleeding in patients with hereditary hemorrhagic telangiectasia (HHT) occurs because of malformations of small veins in the skin and mucosa (telangiectases). Transmission of HHT is autosomal dominant, with males and females affected equally (incidence 1/50,000) [18]. Epistaxis and gastrointestinal (GI) tract bleeding are the most common presentations. The lesions of HHT usually become clinically significant during the second or third decade of life. Examination may reveal lesions in the mouth, face, hands, and feet. The lesions are 1–3 mm in diameter, non-pulsatile, red to purplish and flat, round, or spiderlike. HHT lesions are also found in the lungs of 15–20 % of patients and can occur in virtually any organ.

The diagnosis of HHT is established via the history and clinical examination. The family history is often positive. Screening coagulation studies are usually normal. Therapy for HHT is symptomatic. Whenever possible, pressure is applied to bleeding sites. Cautery or surgical therapy of nasal mucosal lesions yields mixed results. GI bleeding can be treated by resection or embolectomy. HHT is not preventable.

The family and community issues are similar to those faced by patients with other bleeding disorders.

Vasculitis

Vasculitis (vascular inflammation) can be caused by many disease processes, including immune causes, infections, drugs, neoplasms, connective tissue diseases, and cold exposure. Henoch-Schönlein purpura (HSP) (allergic purpura) is considered the model for the study of vasculitis. It primarily affects the kidneys, GI tract, and joints. The etiology is unknown. HSP has been seen after viral and streptococcal infections. Drugs (sulfonamides and penicillin) have been implicated as causative agents, and there are data to support an immune mechanism as a cause [19]. HSP is most often seen in children aged 2–10 years (male/female ratio 2:1) but can occur at any age. There is an increased incidence during early spring and early autumn.

HSP presents with fever followed by a macular or urticarial rash on the buttocks, legs, and arms that becomes purpuric. Lesions can occur in crops. Other findings include edema (legs, hands, scalp, eyes), abdominal pain, vomiting, diarrhea, intussusception, arthritis, and hypertension. Kidney involvement is manifested by proteinuria, hematuria, renal failure, or nephrotic syndrome. Iritis, pericarditis, pleurisy, and neurologic disorders are seen less frequently.

Most patients recover spontaneously within 1 month, although relapses are frequent. Treatment is symptomatic. Penicillin is often used because of the association of HSP with streptococcal infections. Glucocorticoids and immunosuppressive agents can be used for the 5–10 % of patients who develop progressive renal failure. Dapsone is being studied as a possible treatment for HSP [20].

Emergent Bleeding Disorders

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) is a consumptive coagulopathy. Due to a severe underlying cause, there is an acceleration of fibrin deposition in blood vessels and lysis of red blood cells. This disorderly production of fibrin deposition leads to diffuse and damaging fibrin plugs in the microvasculature, further accelerating the process. The fibrin (and procoagulants) is consumed to the point where bleeding occurs. It is a hemorrhagic complication of many serious illnesses (Table 9). Hemorrhage may occur in the skin, central nervous system (CNS), GI system, genitourinary system, or elsewhere. DIC may be

Table 9 Causes of disseminated intravascular coagulation

Tissue injury	Immunologic phenomena
Obstetric problems	**Drugs**
Amniotic fluid embolism	Fibrinolytic agents
Abruptio placentae	Ancrod
Uterine rupture	Warfarin (Coumadin)
Eclampsia	Heparin
Retained dead fetus	Lipid emulsion
Septic abortion	Clotting factor concentrate
Midtrimester abortion	**Other causes**
Malignancies	Liver disease
Infections	Pancreatic disease
Bacterial	Pulmonary disease
Fungal	Neurologic disease
Viral	Envenomation
Protozoal	Transfusions
Cardiovascular disease or injury	

associated with a high mortality rate depending on the nature and severity of the cause. The diagnosis is suspected clinically and confirmed by laboratory findings of elevated fibrin degradation products, prolonged prothrombin and partial thromboplastin times, decreased fibrin levels, and thrombocytopenia.

Treatment of DIC consists of maintaining the vital functions of the patient and treating the underlying disease process. Heparin is used if there is evidence of thrombosis (gangrene of the extremities or digits) [21]. Because DIC depletes coagulation factors, replacement with cryoprecipitate may be considered if there are no evidence of thrombosis and indications of coagulation factor depletion. Platelets are replaced for any patient with a count less than 20,000/mm^3 or any patient with a count less than 50,000/mm^3 with bleeding [22].

Neutropenia

Neutropenia exists when an absolute neutrophil count (ANC) is less than 1500/mm^3 (Table 10):

Table 10 Classifications of neutropenia

ANC	Level of neutropenia	Implication
1000–1500/mm^3	Mild	Increased risk of bacterial infections
500–1000/mm^3	Moderate	Increased risk for opportunistic bacterial infections
<500/mm^3	Severe	Life-threatening bacterial infections common

$$\text{ANC} = \text{WBC} \times (\%\text{Bands} + \%\text{Mature Neutrophils}) \times 0.01$$

This range holds true for both sexes and many ethnicities except in children <12 months of age when neutropenia is defined by an ANC <1000/mm^3. Those of African descent, Jewish Yemenites, and some Arab populations typically have a lower ANC than other nationalities, typically 1400/mm^3, but have very rarely ANC <1000/mm^3 [23, 24]. The diagnosis is confirmed by repeat CBC with manual differential and peripheral smear. Neutropenia can result from decreased production, increased destruction, and margination or shift of neutrophils from blood to tissue. When anemia, thrombocytopenia, and/or abnormal peripheral smear is found in addition to neutropenia, then a bone marrow aspiration could provide evidence of blood cell line disorder or bone marrow failure. Treatment of all causes of neutropenia often requires consultation with hematology. If the patient is febrile in addition to being neutropenic, broad-spectrum antibiotics should be started while awaiting consultation and culture speciation and antibiotic sensitivity. Granulocyte colony-stimulating factor (G-CSF) can be provided to stimulate production of neutrophils acutely to decrease length of neutropenic fever as well as chronically for treatment of neutropenia.

Acquired Neutropenia

Postinfectious Neutropenia

This is the most common cause of acquired neutropenia. Infectious precipitating state can be bacterial or viral. *Staphylococcus aureus* and

Escherichia coli are two common bacteria that can be associated with neutropenia. Common viruses include Epstein-Barr virus, hepatitis B, cytomegalovirus, and influenza which lead to mild or moderate neutropenia. Neutropenia is common among patients with acquired immunodeficiency syndrome (AIDS). When infection is widespread such as in sepsis, neutropenia can be more severe. ANC normalizes as the infection resolves and viremia decreases.

Drug-Induced Neutropenia

Table 11 lists agents associated with neutropenia. Drug-induced neutropenia is the second most common cause, with an incidence of 2.4–15.4 cases per million reported each year. The most common drugs to cause severe agranulocytosis are clozapine, antithyroid drugs (thioamides), sulfamethoxazole-trimethoprim, and sulfasalazine [25]. Treatment is immediate cessation of the medication and consultation with hematology if neutropenia does not improve after the offending drug is discontinued.

Congenital Neutropenia

There are numerous forms of congenital neutropenias, with recessive and autosomal dominant cases, but the most severe is Kostmann syndrome. Kostmann syndrome is diagnosed by persistent ANC $<200/mm^3$ with a history of recurrent infections often of the mouth and perirectal area shortly after birth, fever, organ abnormalities, and short stature. Mutations of the G-CSF receptor are commonly associated with this syndrome. Given the severe nature of the disease, patients are often treated with G-CSF life-long.

Autoimmune Neutropenia

Primary autoimmune neutropenia is the most common cause of neutropenia in children <2 years old [26]. This is often familial and

Table 11 Drugs that cause neutropenia

Nonsteroidal anti-inflammatory drugs	**Antimicrobials (cont)**
Ibuprofen	Capreomycin
Indomethacin	Carbenicillin
Meclofenamate	Cefaclor
Mefenamic acid	Cefadroxil
Oxyphenbutazone	Cefamandole
Phenylbutazone	Cefazolin
Anticonvulsants	Cefotaxime
Carbamazepine	Cephalexin
Mephenytoin	Cephaloglycin
Paramethadione	Cephaloridine
Phenobarbital	Cephalothin
Phenytoin	Cephradine
Valproate	Chloramphenicol
Antipsychotics	Clindamycin
Acetophenazine	Cyclacillin
Carphenazine	Dapsone
Chlorprothixene	Demeclocycline
Antipsychotics (cont)	Doxycycline
Fluphenazine	Flucytosine
Haloperidol	Furazolidone
Loxapine	Griseofulvin
Mesoridazine	Hetacillin
Molindone	Lincomycin
Perphenazine	Methacycline
Piperacetazine	Metronidazole
Thiethylperazine	Mezlocillin
Thioridazine	Moxalactam
Thiothixene	Nafcillin
Trimeprazine	Novobiocin
Trifluoperazine	Oxacillin
Triflupromazine	Oxytetracycline
Antidepressants	Para-aminosalicylic acid
Amitriptyline	Penicillin G
Amoxapine	Penicillin V
Desipramine	Pyrimethamine
Doxepin	Quinine
Imipramine	Quinacrine
Nortriptyline	Rifampin
Protriptyline	Tetracycline
Maprotiline	Ticarcillin
Trimipramine	Trimethoprim
Antiarrhythmics	Vidarabine
Procainamide	Zidovudine
Quinidine	**Antineoplastic agents**

(*continued*)

Table 11 (continued)

Tocainide	**Other drugs**
Anxiolytics	Allopurinol
Diazepam	Clofibrate
Tybamate	Dantrolene
Diuretics	Ethanol
Diazoxide	Levamisole
Ethacrynate	Levodopa
Mercaptomerin	Methyldopa
Antimicrobials	Methysergide
Amoxicillin	Nifedipine
Ampicillin	Penicillamine
Bacampicillin	Podophyllin
	Sulfonamides

characterized by the patient's inability to increase WBC count when ill. The patient will still show clinical signs of illness such as tachycardia and fever. Children with this diagnosis will usually have resolution without intervention within 2–3 years, and all patients often recover by 5 years old.

Patients with secondary autoimmune neutropenia will often have positive antineutrophil antibodies (ANA). Common comorbid diagnoses include Crohn's disease, systemic lupus erythematosus, Felty syndrome, antiphospholipid antibody syndrome, and rheumatoid arthritis. Other primary causes of secondary autoimmune neutropenia include infection and malignancy. Those with lupus and Felty syndrome may improve with splenectomy or immunosuppressive therapy.

Alloimmune (Isoimmune Neutropenia)

Isoimmune neutropenia occurs in 3 % of live births and is caused by maternal antineutrophil antibodies to fetal neutrophil antigens. Associated clinical manifestations include neonatal fever; infection within the urinary tract, skin, and lungs; or signs of sepsis. Neutropenia is likely to resolve within 7–15 weeks. Treatment options range from glucocorticoids and/or IgG antibodies to exchange transfusion with maternal neutrophils that may be warranted.

Nutritional Neutropenia

Neutropenia can be caused by deficits of vitamin B_{12}, folate, and copper, all of which are common in patients who abuse alcohol. Neutropenia can resolve with adequate supplementation of vitamin deficits.

Intrinsic Defects Causing Neutropenia

Cyclic neutropenia is associated with periodic bouts of neutropenia and infection, followed by return to normal levels of neutrophils. As in other hereditary neutropenic disorders, the underlying etiology is a genetic mutation affecting neutrophil elastase (ELA2). Counts cycle on average every 21 days. Many are genetically inherited and present in infants and children but can be acquired in adulthood. Treatment is supportive to include antimicrobial mouthwash when neutropenia is mild to daily G-CSF if neutropenia is severe.

Other Hematologic Disorders

Hemochromatosis

Hereditary hemochromatosis (HH) is an autosomal recessive inherited disorder in patients of European origin with an increased prevalence in men. Age at diagnosis is typically 40–60 years old, relatively later in women compared to men due to blood loss associated with menstruation. It is estimated that 1–6 people per 100 in the United States will have elevated transferrin levels, 35–50 % of those will have persistent elevation, and less will have concurrent ferritin elevation and even fewer develop clinical symptoms [28]. Eighty to 90 % of those patients diagnosed with hereditary hemochromatosis are homozygous for the HFE gene C282Y, and 10 % of those will have end-organ damage associated with the disease [29]. Secondary

hemochromatosis is common among anemias that are associated with iron absorption and inefficient erythropoiesis, as well as a requirement of chronic transfusions. Patients are typically asymptomatic if caught early, but as iron overload progresses clinical manifestations include cardiomyopathy, dysrhythmias, cirrhosis of the liver, hepatocellular carcinoma, bronzing of the skin, diabetes, arthralgias, osteoporosis, and hypogonadism.

Non-fasting serum levels of ferritin and transferrin saturation (serum iron concentration divided by total iron-binding capacity in mcg/dL then multiplied × 100) can be used to screen for diagnosis. Per the 2011 guidelines from the American Association for the Study of Liver Diseases, the recommended cutoffs of >45 % transferrin saturation and serum ferritin >300 ng/mL in men and >200 ng/mL in women could indicate disease [30]. An elevated transferrin saturation has greater sensitivity than a plasma ferritin for detecting HH [31]. When transferrin saturation cutoff is increased from >45 % to >50 %, the specificity for recognizing someone homozygous for C282Y increases from 0.96 to 0.98 [32]. Definitive diagnosis is made following pathologic evaluation of a liver biopsy which is needed to stage fibrosis and diagnose nonclassical hereditary hemochromatosis [29].

Treatment of hereditary hemochromatosis entails regular phlebotomy to decrease serum ferritin levels to 50–150 ng/mL while maintaining an Hgb >12.5 g/dL [33]. If secondary hemochromatosis is present, then iron chelation is preferred to phlebotomy given typical levels of anemia already present in those with secondary hemochromatosis. Six percent of individuals with HH and cirrhosis will develop hepatocellular carcinoma; therefore patients should have screening liver ultrasonography every 6–12 months [34]. Intervals of scans are decreased even further if lesions are found on the liver. Screening for disease outside of symptoms or evidence of iron overload is only recommended for those with first-degree relatives with hereditary hemochromatosis [35]. Dietary modifications need not be made but oral iron supplementation and vitamin C should be avoided.

Polycythemia

Polycythemia vera is a chronic myeloproliferative disorder resulting in HCT >52 % in white men and HCT >47 % for women and African Americans [36]. Evidence of portal vein thrombosis and splenomegaly with or w/o thrombocytosis or leukocytosis should increase clinical suspicion of the diagnosis. Low serum erythropoietin (EPO) has a sensitivity of 70 % and a specificity of 90 % for polycythemia vera. The median age at diagnosis is 60 years old, and incidence of disease is 2.3/100,000 persons per year with a slightly higher incidence in men compared to women [36]. Classic clinical symptoms are pruritus after bathing, burning pain in distal extremities, weakness, and gastrointestinal symptoms. It is important to recognize and refer immediately as survival is greater than 10 years if treated with regular phlebotomy and myelosuppressive agents but is 6–18 months without treatment [36]. Mortality from disease is secondary to vascular thrombosis from increased number of RBCs. Goal of phlebotomy is to maintain an HCT <45 % in white males and <42 % in women and African Americans.

Secondary polycythemia can arise from underlying lung or heart disease, living at high altitude, or smoking. If concurrent hypoxia is associated with lung or heart disease, then RBC counts will decrease with supplemental oxygen. There is no way to prevent polycythemia vera, but one can prevent secondary polycythemia by preventing heart and lung disease by things such as tobacco cessation.

Sickle-Cell Disease

Sickle-cell anemia is an autosomal recessive inherited disease caused by a single defect in the beta chain of hemoglobin (Hb A) resulting in sickle hemoglobin molecule (Hb S) that becomes dysfunctional when deoxygenated. Patients who are homozygous for the sickle-cell gene have sickle-cell anemia (Hb SS), and those who are heterozygous have sickle-cell trait (Hb S trait). Sickle-cell disease includes multiple common genotypes (Hb SS, Hb S beta$^{0 \text{ and } +}$ thalassemia,

and Hb SC) and resulting phenotypes. Sickle-cell disease affects 70,000–100,000 people in the United States of predominantly African and Hispanic descent [37]. On average 2000 infants are born with the disease each year [37].

Morbidity and mortality stem from chronic hemolysis, tissue infarction, and painful episodes. Vaso-occlusion episodes not only involve the sickled RBC but also leukocytes, activated vascular endothelium, altered nitric oxide metabolism, hypercoagulability, and ischemia-reperfusion injury [38]. Individuals with Hb SS have marked clinical manifestations with associated morbidity and mortality, while those with Hb S trait are relatively asymptomatic. The other common genotypes of sickle-cell disease detailed above are associated with mild to moderate clinical symptoms.

Mortality from sickle-cell disease fell by 42 % in African American children under 4 years old following addition of pneumococcal vaccination in 2000 [39]. Survival rates have increased from 14 years old to nearly 50 years old within one generation secondary to vaccines and prophylactic antibiotics [40]. Patients are at increased risk for infection from encapsulated organisms secondary to splenic dysfunction. All infants with Hb SS and Hb SB^0 thalassemia should receive daily penicillin starting at 2 months of age. It is more controversial to give daily penicillin for prophylaxis in infants with Hb SC and Hb SB^+ [41]. Erythromycin is the preferred alternative antibiotic, and if there is no history of invasive pneumococcal disease or splenectomy, then prophylaxis can be stopped at 5 years old. Concern for infection requires initiation of broad-spectrum antibiotics and then tailored to organism as appropriate. As detailed below transfusions to maintain Hgb >10 g/dL improve morbidity perioperatively in all but lowest risk surgeries, as do chronic transfusions reduce the incidence of primary stroke by 1.6 % of abnormal transcranial blood flow velocity (TBV) on transcranial Doppler ultrasonography [40]. Other reasons for acute transfusion include: splenic or hepatic sequestration, stroke, multiorgan failure, and worsening acute chest syndrome, while additional reasons for chronic transfusions include prevention of stroke recurrence, chronic heart failure, pulmonary hypertension, or recurrent splenic sequestration. Side effects of recurrent transfusions include iron overload, which can comparably be managed with oral deferasirox as with IV deferoxamine [37].

Acute manifestations of the disease include painful crises, acute chest syndrome (ACS), and multiple organ failure syndrome. Painful crises are managed with opiates to control pain but not over sedate (ketorolac is an ineffective adjunct to narcotics) [37] and meperidine should be avoided [40], oxygen if hypoxic, frequent incentive spirometry and fluid overload avoidance to prevent progression to acute chest syndrome. Patients with acute chest syndrome present with dyspnea, cough, chest pain, fever, and a new infiltrate on chest radiography. Treatment with dexamethasone may limit severity of ACS in children but has been correlated with rehospitalization within 72 h of discharge for severe pain [44]. When conservative management fails to improve hypoxemia or signs of respiratory failure occur, then transfusion of pRBCs is warranted. Fever, worsening anemia, decreased platelets, rhabdomyolysis, and mental status changes are all associated with the onset of multiorgan failure. Rapid referral to a specialist is warranted as exchange transfusion could be lifesaving [46] (Table 12).

As with management of all chronic diseases, physicians should expect both the patient and family to go through significant adjustments to the diagnosis and management of the disease. Many aspects of this adjustment correspond to those typically seen in a grief-loss process. Physicians and families must encourage the patient to be as active and involved as possible, promoting independence and confidence in his or her abilities as well as decreasing withdrawal, regression, and the potential for depression. Independence also minimizes the tendency for anger and resentment to build up if the patient-family relationship becomes overly dependent. Problems can arise when family members try to protect the patient and consistently put the needs of the patient first becoming attentive to their every need. The decision to take on these functions is often made without an overt discussion within the family.

Table 12 Treatment for patients with sickle-cell disease

General treatment
Caloric supplements
Folic acid (5 mg/day) – remains controversial
Prophylactic penicillin, daily starting at 2 months old until 5 years old unless there is h/o invasive pneumococcal disease or splenectomy
Pneumococcal vaccine (7-valent conjugate vaccine prior to 2 years old, 23-valent polysaccharide vaccine when >2 years old, redose in q3–5 years revaccination when <10 years old or in 5 years if initial dose >10 years old)
Haemophilus influenzae B vaccine, annual influenza, and quadrivalent meningococcal after 2 years old
Hepatitis B vaccine
Transfusions to maintain hemoglobin between 10 and 12 g/dL, especially prior to surgery
Chelation therapy as needed for iron overload
Antidepressants for chronic pain
Psychological support
Acute crisis treatment
Hydration (IV hypotonic fluids for maintenance after volume resuscitation achieved)
Oxygen if hypoxic, incentive spirometry, or positive expiratory pressure device for all during waking hours
Antibiotics if fever or infection is present
Analgesia: consider patient-controlled analgesia with narcotics (narcotics preferred over NSAIDS)
Crisis prevention
Hydroxyurea – adults, adolescents, and emerging research in kids with 3+ moderate to severe vaso-occlusive episodes per year (use decreases painful crises, acute chest episodes, and frequency of transfusions)
Transcranial Doppler ultrasonography – screening at 2 years old to identify those with abnormal transcranial blood flow velocity (TBV). If TBV is elevated child has increased risk from stroke, and prophylactic transfusions can prevent primary stroke
Allogeneic hematopoietic cell transplantation – indicated in young patients with multiple sickle-cell disease-related complications; studies have shown that it can be curative

Power struggles can ensue and can manifest in various behavioral-emotional symptoms (i.e., school problems, family dysfunction, caregiver burnout). Pain associated with a chronic, relapsing condition like sickle cell can be one of the most troubling symptoms patients and their families confront and the most difficult for physicians to manage [46–48]. This is because chronic pain is a subjective experience involving the interactions among physiologic, psychological, and sociocultural factors. Chronic pain can have its origins not only in the organic disease but also in the patient's psychological distress (i.e., anxiety, depression, substance abuse), caregiver burnout, and/or secondary gain (i.e., malingering). The diagnostic question that emerges is: How much of this pain is real and how much is psychological? The physician can sort out the issues and answer this question by taking a careful history, paying attention to the patient's affect and caregivers' verbal and nonverbal signals, assessing the patient for psychosocial problems, and maintaining continuity of care.

It is critical that all family members be given adequate and clear information regarding the nature of the disease. Major decisions about caregiving, symptom management, and range of activities should be negotiated, with physician assistance if necessary. Ultimately, families are helped by the physician assisting them to live with and not be consumed or defined by the chronic condition.

Hematologic Malignancies

Multiple Myeloma

Multiple myeloma (MM) is the most common bone malignancy characterized by expansion of plasma cell mass and overproduction of M proteins (IgG, IgM, or IgA or rarely IgE or IgD). The number of new cases diagnosed is 6.1 per 100,000 men and women per year [49]. Median age at diagnosis is 70 years old, and incidence increases with age. The diagnosis is more common among males than females and African Americans more than Caucasians. Clinical symptoms include bone pain, malaise, anemia, recurrent infections, renal insufficiency, and hypercalcemia. Initial workup when diagnosis is suspected includes CBC, CMP, ESR, and serum and urine protein electrophoresis in addition to X-rays of the chest, long bones, pelvis, and skull.

The diagnosis of symptomatic MM is made by presence of characteristic serum and urine M proteins by electrophoresis or immunofixation and

bone marrow clonal plasma cells in addition to end-organ impairment (hypercalcemia, renal insufficiency, anemia, and bone lesions). MRIs are used to assess for spinal cord compression or soft tissue plasmacytomas. A premalignant disorder known as monoclonal gammopathy of undetermined significance (MGUS) also leads to increased monoclonal paraproteins, but unlike those associated with multiple myeloma, they do not cause end-organ damage and do not require treatment. Symptomatic MM is treated with systemic chemotherapy and if they are young and well enough autologous stem cell transplantation. All of those with symptomatic MM should be prescribed a bisphosphonate (IV preferred), level of evidence A, to decrease vertebral fractures and pain [50]. Bone pain is best managed with opiates. Percutaneous vertebroplasty and kyphoplasty improve symptoms associated with comorbid vertebral compression fractures. Relapse is common, and according to the American Cancer Society, median survival is anywhere from 29 to 62 months depending on stage at diagnosis [51].

Myelodysplastic Syndromes

Myelodysplastic syndromes (MDS) are disorders associated with the neoplastic development of stem cells resulting in abnormalities of hematopoiesis. Individual or various cell lines can be affected resulting in symptomatic anemia (most common), increased bleeding secondary to thrombocytopenia, or increased risk of infection secondary to neutropenia. Some patients with MDS will progress to have acute myelogenous leukemia. Many cases are associated with treatment from a previous malignancy, but many arise without etiology. The incidence rate during 2001–2004 within the United States was roughly reported to be 3.3 per 100,000, but the diagnosis is often underreported [52]. Prevalence is higher among males than females and increases with age. Patients are more likely to be found in those of Caucasian or Hispanic origin. The age-adjusted 3-year survival rate for MDS is approximately 60 % [53].

Peripheral blood smears will often demonstrate dysplasia, and % of blasts to determine involvement and specific histologic features of the cells can be determined from a bone marrow biopsy. MDS is commonly diagnosed based upon unexplained cytopenia (Hgb <10 g/dL, absolute neutrophil count $<1.8 \times 10^9$/L, or platelets $<100 \times 10^9$/L), morphologic dysplasia, and blast cells accounting for less than 20 % of total cells on the bone marrow aspirate and peripheral blood smear. Aside from allogeneic hematopoietic cell transplantation, there is no cure for MDS. Systemic chemotherapy, erythropoietin, hematopoietic growth factors, and immunosuppressive therapy are common agents utilized for management of disease. Asymptomatic patients do not necessarily need treatment, and immediate treatment/referral to a hematologist is warranted for symptomatic anemia and/or thrombocytopenia or recurrent infections secondary to neutropenia.

Leukemias

Leukemias are the result of massive proliferation of hematopoietic stem cells. They are categorized as acute or chronic and lymphoblastic or myelogenous. The age-adjusted incidence rate of leukemia within the United States in 2011 (for all races and both sexes) was 13.66 per 100,000 persons [54]. Roughly 1 in 70 persons will develop leukemia in their lifetime [55]. The prevalence of the disease increases with age, and more white males will be diagnosed than females or other ethnicities. Of the four classifications (listed in Table 13), ALL is the most common childhood cancer, and 80 % of leukemias among adults are AML. Predisposing risk factors for the disease include many genetic abnormalities (Down syndrome, neurofibromatosis), immunodeficiency disorders, exposure to ionizing radiation, industrial chemical exposure (i.e., benzene), and previous leukemia or radiation therapy.

Common presenting signs of leukemia are fever of unknown origin, anorexia, pallor, lethargy, and abnormal bleeding or bruising. One-third of all children will present with long-bone or spine pain that wakes them up, and 75 %

Table 13 Leukemias [55]

Disease	Incidence	Treatment	5-year survival rate
Acute			
Acute myeloid leukemia (AML)	Common in elderly; 80 % of acute leukemia in adults	Systemic chemotherapy Bone marrow transplantation (selected patients)	<50 years old = 55 % >50 years old = 14 %
Acute lymphocytic leukemia (ALL)	Common cancer in children, 53 % of new cases <20 years old	Systemic chemotherapy Bone marrow transplantation (selected patients)	<50 years old = 75 % >50 years old = 25 %
Chronic			
Chronic myeloid leukemia (CML)	More common in middle age	Systemic chemotherapy Bone marrow transplantation (selected patients) Splenic irradiation (selected patients)	<50 years old = 84 % >50 years old = 48 %
Chronic lymphocytic leukemia (CLL)	More common in the elderly (>65 years old)	Systemic chemotherapy Radiation therapy (selected patients)	<50 years old = 94 % >50 years old = 83 %

of children with leukemia will have hepato- or splenomegaly. Priapism is a red flag for childhood leukemia [56]. Adults will have the common presenting signs detailed above in addition to weight loss and anemia-related symptoms such as dyspnea or chest pain. If diagnosis is suspected, a CBC is drawn first; a complete metabolic panel and coagulation panel are helpful for any concurrent abnormalities and will give the hematologist/oncologist baseline liver functions. In current level evidence rating of C, all patients with a WBC >20,000 per uL and associated anemia, thrombocytopenia, thrombocytosis, or hepato- or splenomegaly or constitutional symptoms need to have a peripheral smear ordered [55]. Any positive lab findings in light of symptoms require prompt referral to a hematology/oncology specialist.

ALL and AML treatment may include chemotherapy, radiation, monoclonal antibodies, or hematopoietic stem cell transplant. CLL may be just monitored if there are no anemia or thrombocytopenia and less than three areas of nodal involvement, and CML progression can be slowed with tyrosine kinase inhibitors, but definitive treatment is with hematopoietic stem cell transplant [55]. When cranial irradiation is used to treat ALL, growth hormone deficiency and metabolic syndrome are common resulting disorders [57]. As more and more children with leukemia are surviving, it has become important for the family physician to be able to care for these cancer survivors. In addition to any age-appropriate USPSTF cancer screening guidelines, a leukemia survivor should have 1–2 months CBCs for the first 3 years, then every 3–6 months for up to 5 years, and then annually [55]. The most common form of cancer after diagnosis of leukemia is another form of leukemia or lymphoma. From a cohort of 17,000 childhood cancer survivors in North America treated between 1970 and 1986 as part of the Childhood Cancer Survivor Study, the 30-year cumulative occurrence of cancer after leukemia was 5.6 % [58]. 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. Knowing the chemo agent used is helpful, especially if an anthracycline (such as

doxorubicin) was used as 5–10 % will develop congestive heart failure 20–30 years after treatment [57]. Follow-up care for both acute leukemias includes an echocardiogram every 2–3 years; however, echocardiograms are not routinely monitored for those who had or who have chronic leukemia.

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Selected Disorders of the Eye

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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. 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 a picture chart or matching chart [3]. Along with visual acuity, confrontation visual fields, ocular motility testing, ophthalmoscopy, corneal staining, pupillary examination, and pressure measurement are essential elements of a complete urgent exam [1].

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 iris 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 [2].

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 [2].

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) [3].

Positional Abnormalities

Entropion

Entropion is 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, tearing, and blepharitis. Treatment includes eyelid hygiene, lubricating agents, and topical antibiotics when inflammation is present. Taping or patching can be palliative or temporary while awaiting definitive surgical procedures for symptomatic patients [4].

Ectropion

Eversion of the lid margin, or ectropion, can be age related, cicatricial, spastic, and allergic. Severe cases may follow Bell's palsy (see chapter "▶ Care of the Patient who Misuses Drugs"). 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 (see chapter "► Selected Disorders of the Female Reproductive System"). 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].

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 removal of the offending agent (see chapter "► Selected Disorders of the Female Reproductive System"). 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 etiologies 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].

Pingueculum and Pterygium

A pingueculum is an area of 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.

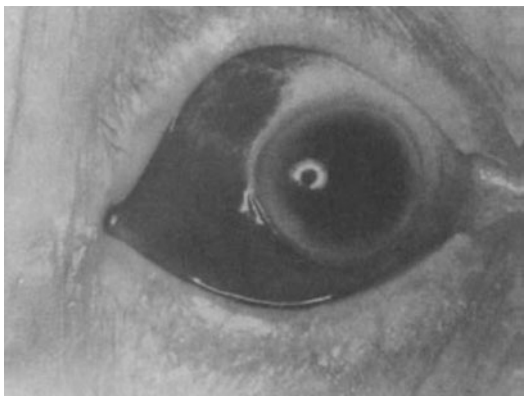

Fig. 1 Subconjunctival hemorrhage

Occasionally inflammatory discomfort of either a pingueculum or pterygium may require a mild topical steroid or nonsteroidal anti-inflammatory drop [2].

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 [2, 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 include muscle weakness, allergy, ectropion, occlusive scarring, glaucoma, dacryocystitis, canaliculitis, and inflammation [2]. 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 [3].

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 (see chapters "▶ Benign Breast Conditions and Disease" and "▶ Selected Disorders of the Musculoskeletal System"). 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. The Schirmer and rose bengal test results do not have a significant

association with symptoms [11]. 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 [7, 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 [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 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 (see chapter "▶ Epstein-Barr Virus Infection and Infectious Mononucleosis"). 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, 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].

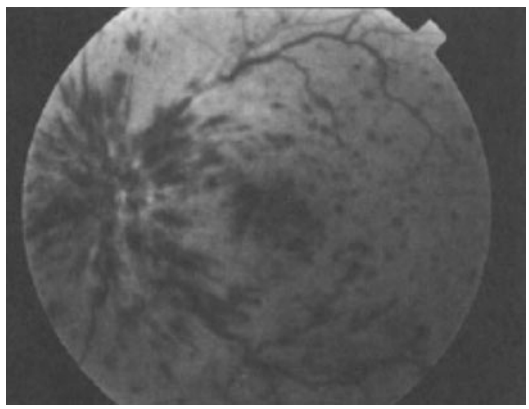

Fig. 2 Central retinal vein occlusion

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, a flame-shaped hemorrhage is present upon examination [14]. Treatment involves intravitreal injections of anti-vascular endothelial growth factor (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 a 1 % chance of a retinal detachment. Retinal detachment can occur in about 10 % of patients with 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 (see chapter "▶ Rheumatoid Arthritis and Related Disorders").

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].

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].

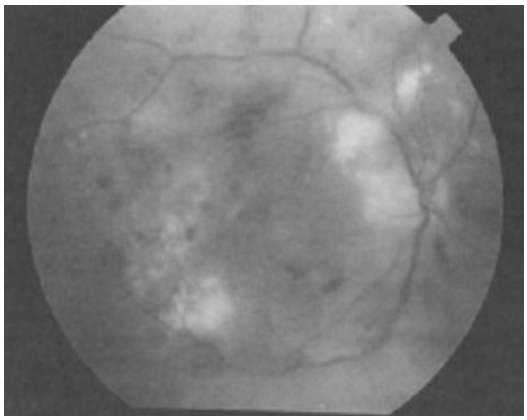

Fig. 3 Nonproliferative diabetic retinopathy

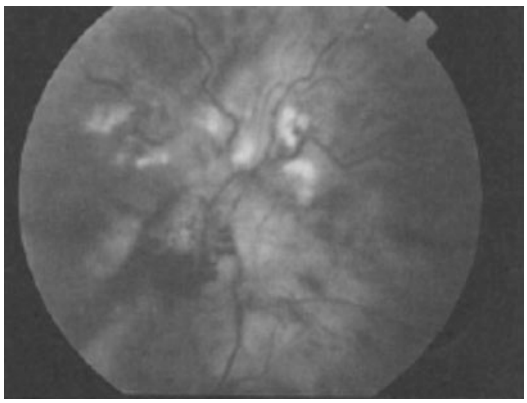

Fig. 4 Proliferative diabetic retinopathy

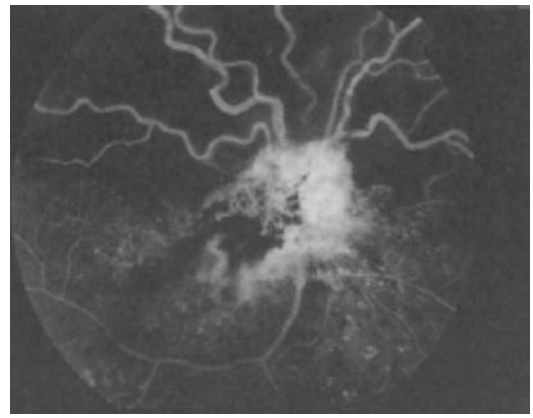

Fig. 5 Angiogram of proliferative diabetic retinopathy

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, is undertaken [1].

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 (see chapter "► Care of the Patient with a Sleep Disorder"). 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 [1, 14].

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].

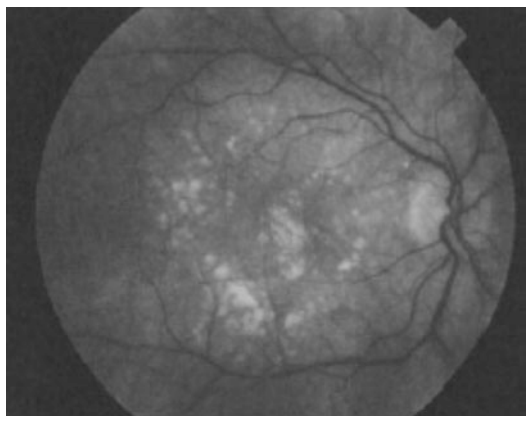

Fig. 6 Dry age-related macular degeneration

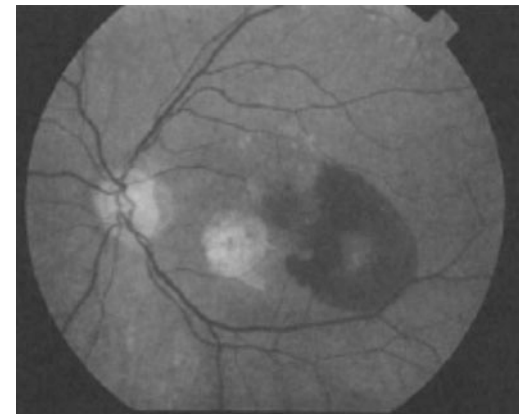

Fig. 7 Wet age-related macular degeneration

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

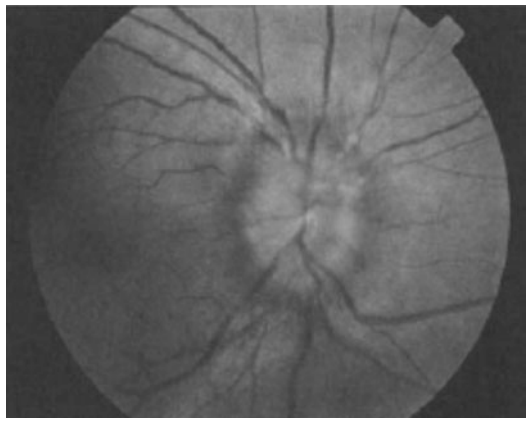

Fig. 8 Optic nerve head edema (papilledema)

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].

Lens

Cataracts, or a clouding of the lens of the eye, are increasingly common among our aged population in the United States. The cataract can be graded in three of the most common varieties, based on the location of the lenticular opacity.

A nuclear sclerotic cataract is 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 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 2004, the prevalence of POAG for adults 40 and older in the United States was estimated to be about 2 % [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, 23–26].

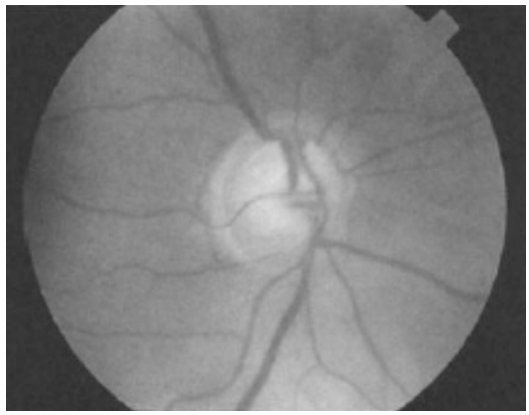

Fig. 9 Chronic open-angle glaucoma with loss of axons; note the centrally excavated optic cup

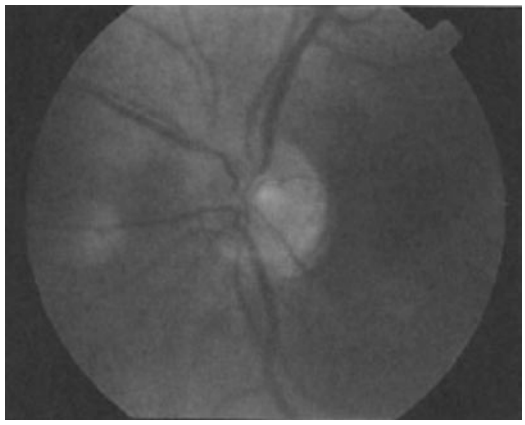

Fig. 10 Normal optic nerve with a healthy, nonexcavated optic cup

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. Examine the eyes of newborns and children for symmetric corneal light reflex and use the cover/uncover test to identify esotropia (in-turning of one eye) or exotropia (out-turning of one eye). At birth most infants have a small degree of exotropia that resolves during the first few months of life. Newborns 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 [3].

The treatment of strabismus is based on first correcting any refractive disorder, patching for amblyopia if present, and, lastly, surgically realigning the eyes. Visual outcome is best when the problem is diagnosed early [3, 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 ft 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 [3, 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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