

# Infectious Disease in the Aging

*A Clinical Handbook*

**SECOND EDITION**

Edited by

**THOMAS T. YOSHIKAWA**

**DEAN C. NORMAN**

# Infectious Disease in the Aging

# Infectious Disease

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A Clinical Handbook

Second Edition

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*To our wives,  
Catherine Yoshikawa and Jane Norman,  
for their love and support*

## Preface to the Second Edition

Since the first edition of *Infectious Disease in the Aging: A Clinical Handbook*, the problem of infections in older adults remains a clinical challenge for primary care physicians, geriatricians, infectious disease specialists, surgeons and other surgical specialists, pharmacists, and providers working in long-term care facilities, all of whom care for elderly patients. Despite the availability of improved diagnostic techniques and newer antimicrobial agents, the common and well-recognized infectious diseases of geriatric patients such as pneumonia, urinary tract infections, skin and soft tissues infections, osteomyelitis, septic arthritis, tuberculosis, intraabdominal sepsis, bacterial meningitis, and infective endocarditis continue to cause serious morbidity and mortality. Furthermore, in the aging population, “newer” infections have appeared that are particularly common and/or more severe; these include acute respiratory syndrome and West Nile virus infection. As the aging population increases and people are living longer, infections that occur more frequently in younger adults become increasingly more important in older adults, such as human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS). Finally, with the increasing prescription of antibiotics, the prevalence of antimicrobial resistance is accelerated at an alarming rate. Infections caused by *Staphylococcus aureus* are now primarily due to methicillin-resistant strains (MRSA). MRSA infection is a major infectious disease problem in older patients.

In this second edition of *Infectious Disease in the Aging: A Clinical Handbook*, the editors have once again assembled the leading experts in geriatric infectious disease; we have updated all the chapters, added new chapters, and included new references. The information, including tables and figures, is presented succinctly but completely. The editors feel that readers will continue to find this textbook a valuable and important resource for diagnosing and managing infections in older adults as well as a reference guide for training, educating, and for developing policies and procedures for infection control. As we stated in our first edition, we again welcome your comments and suggestions.

Los Angeles, CA

Thomas T. Yoshikawa  
Dean C. Norman

## **Acknowledgements**

The editors wish to thank all of the contributing authors, who made this book a reality. We also want to extend our gratitude to Ms. Patricia Thompson for typing and retyping the manuscripts.



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**Part I**  
**Concepts and Principles of**  
**Infections and Aging**



# Epidemiology of Aging and Infectious Diseases

Thomas T. Yoshikawa

## Key Points

- The increase in life expectancy, resulting in the growth of the elderly population during the twentieth century, occurred because of the reduction of mortality and morbidity that was caused by infectious diseases.
- Ironically, with aging, infectious diseases have become an important cause of death, disability, and functional incapacity in the geriatric population.
- The most common infections in older adults are lower respiratory tract infections, tuberculosis, urinary tract infections, skin and soft tissue infections, infective endocarditis, intraabdominal infections, bacterial meningitis, herpes zoster, and bacteremia from a variety of causes.
- As the oldest segment of the aging population rapidly expands (i.e., those 80 years and older), and thus requires long-term care, infection in nursing facilities has become an important clinical problem.
- Assessing an older patient's functional capacity before, during, and after an infection should be an essential component of diagnosis and management as well as research in infectious diseases in this population.

## Infectious Diseases and History of Mankind

Throughout recorded history, mankind has always faced the scourges of infectious diseases. Infections were the major causes of mortality prior to the modern era of antimicrobial chemotherapy, and, even today, infectious diseases worldwide account for over one-third of the deaths. Until the mid-twentieth century, such

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diseases as typhus, plague, typhoid fever, cholera, diphtheria, smallpox, and tuberculosis caused major outbreaks of illnesses and accounted for deaths of millions of people throughout the world. Moreover, rheumatic fever, scarlet fever, measles, mumps, pertussis, poliomyelitis, and syphilis not only resulted in mortality but also caused disability, deformities, limitation in functional capacity, and social rejection (1). During the Civil War, infections caused more deaths than battle injuries for both the Confederate and Union armies; similar statistics have been described for combatants in World War II (2). Poor sanitation, close contact, inadequate acquired immunity to diseases, and high stress levels left military combatants vulnerable to typhoid, malaria, dysentery, tuberculosis, smallpox, and measles.

With the establishment of the germ theory of diseases, medical advances followed (i.e., sanitation, public health measures, antiseptics, antibiotics, and immunization) that reduced the mortality and morbidity of infectious diseases after the middle of the twentieth century. Beginning in the last half of the twentieth century, the modern era of antimicrobial therapy and vaccination successes of smallpox and poliomyelitis appear to have heralded the “conquering” of the lethal effects of infections (2). However, in 1981, the first cases of acquired immunodeficiency syndrome (AIDS) were reported by the Centers for Disease Control and Prevention, and, in 1984, AIDS would be identified to be caused by the human immunodeficiency virus (HIV) (2). AIDS has become a global health care problem, striking the young, the old, the rich, the poor, men, women, and people of all ethnic and racial backgrounds. HIV infection and its complications has clearly become the single most publicized and (perhaps) important disease of recent modern times (see also chapter “Human immunodeficiency virus/Acquired immunodeficiency syndrome”). Finally, newer pathogens have emerged during the past one or two decades, (e.g., Hanta virus, Ebola virus, and herpes simplex type 6 as well as mutant strains of antibiotic-resistant organisms such as methicillin-resistant *Staphylococcus aureus* (see also chapter “Staphylococcal and Enterococcal Infections”), penicillin-resistant *Streptococcus pneumoniae*, vancomycin-resistant enterococci (see also chapter “Staphylococcal and Enterococcal Infections”), multiple drug-resistant gram-negative bacilli, and *Clostridium difficile* (see also chapter “Infectious Diarrhea”) (3–6)). The impact of all of these and other new and changing infectious disease agents on both the young and the old in the future will be the interest and focus of many infectious diseases specialists and clinicians caring for children, adults, and the elderly (7).

## Demographics of Aging

In 1900, at birth, the average life expectancy in the United States (U.S.) was approximately 47 years (46 years for males and 48 years for females) (8); only 4% of the total U.S. population was aged 65 years and older (9). With the reduction in childhood mortality, due primarily to infectious diseases, the average life expectancy dramatically increased during the latter half of the twentieth century. Presently, at birth, the average life expectancy in the United States is approximately 75 years

(73 years for males and 80 years for females) (8). Furthermore, the elderly (aged 65 years and older) now account for approximately 13% of the entire U.S. population (9). It is anticipated that over the next 30 years, those persons 65 years and older will account for 21% of all Americans, with the older elderly (80 years and older) experiencing the most rapid growth based on percentage of elderly persons.

## **Epidemiology of Mortality, Infections, and Aging**

### ***Causes of Death***

Up until the beginning of the twentieth century, half of the top 10 causes of death in the United States were attributed to infections. Children, unfortunately, were disproportionately affected. As stated earlier, with the advent of immunization, sanitation, public health practices, antiseptics, and antibiotics, many of the lethal infectious diseases were prevented or mitigated. With the reduction of childhood mortality, life expectancy dramatically increased (see previous discussion). Similarly, there were decreases in infectious disease deaths and complications in adults as well; however with adults living longer, other diseases have now become more common and prevalent. For the entire U.S. population, heart disease, cancer, and stroke are the most common causes of death. In the elderly population, these same three diseases hold the same level of prominence; however, in the elderly, pneumonia and influenza are the fourth leading cause of death; diabetes mellitus and its complication, including infections is the sixth leading cause of death; and bacteremia is responsible for the ninth most common cause of death (10).

### ***Common Infections in the Elderly***

Although older persons are at greater risk for acquiring infections, there are little data that indicate aging is associated with greater susceptibility to all infections. Whether aging alone vs. age-related diseases, which adversely impact host resistance to infections, is responsible for vulnerability to infections remains controversial and unproven (11).

There are considerable data indicating that certain infections appear to occur more often in older persons and are associated with higher mortality and morbidity (12–15). These infections include lower respiratory infections, primarily bacterial pneumonia, urinary tract infections, skin and soft tissues infections, including infected pressure ulcers, tuberculosis, infective endocarditis, sepsis with known and unknown causes, intraabdominal infections, primarily cholecystitis, diverticulitis, appendicitis, and abscesses, bacterial meningitis, and herpes zoster (12). (Specific and in-depth details of these infections can be found in the appropriate chapters.)

**Table 1** Common infections in the elderly and comparative mortality with younger adults

Infections	Mortality rate in elderly vs. young adult
Pneumonia	3 <sup>a</sup>
Tuberculosis <sup>b</sup>	10
Urinary tract infection <sup>c</sup>	5–10
Infective endocarditis	2–3
Intraabdominal infection	
Cholecystitis	2–8
Appendicitis	15–20
Bacterial meningitis	3
Septic arthritis	2–3

Source: Refs. (12, 16, 17)

<sup>a</sup>Indicates that mortality rate is three times greater in elderly compared with young adult

<sup>b</sup>In nonhuman immunodeficiency virus-infected persons

<sup>c</sup>Kidney infection

The majority of these infections, when compared with younger adults with the same disease, are associated with higher death rates in the elderly [Table 1 provides a summary of these findings (12, 16, 17)].

### *Infections in Long-Term Care Setting*

As mentioned earlier, it is anticipated that with the rapid increase in the aging population, there will be a disproportionate growth in the very old segment of this group. With extreme old age, comes frailty, cognitive impairment, and physical dependence. It has been stated that persons aged 65 years and older have approximately 45% risk during their lifetime of becoming institutionalized in a long-term care facility (e.g., a nursing facility (nursing home)) (18). Furthermore, frail elderly residents in nursing facilities are substantially vulnerable to infections because of age-related immune changes, diseases, and physical disabilities (see also chapter “Infections in the Long-Term Care Setting.” A closed, institutional environment also favors constant exposure to microorganisms because of frequent contacts with personnel and other residents, limited ventilation, filtration, and removal of recirculated air, which could contain microorganisms, and the unrestricted movement of infected residents (19).

It is estimated that approximately 1.5 million infections occur annually in nursing facilities in the United States (20). The incidence of infections has been reported to range from approximately 10–20 infections per 100 residents per month (21). The most frequently encountered infections in residents of long-term care facilities are lower respiratory infections (pneumonia most often), urinary tract infections,

and skin and soft tissue infections (including infected pressure ulcers) (see also chapter “Infections in the Long-Term Care Setting”). These three infections constitute nearly 70–80% of nursing facility-associated infections (21). Moreover, fever is one of the most common reasons residents of a nursing facility are transferred to an acute care facility (22); furthermore, infections are often the cause of acute confusion or delirium in older persons (23). Thus, the presence of fever and/or an acute change in clinical/functional status of a resident in a long-term care facility should prompt a careful search for an infectious etiology (22). Finally, the increasing use of antimicrobial agents in residents of long-term care facilities has been associated with an alarming rise in mutant strains of bacteria that are resistant to a variety of antibiotic agents (7). Stringent adherence to infection control policies and to measures of appropriately prescribing antimicrobial agents will be necessary to prevent major outbreaks of life-threatening and untreatable infections (see also chapter “Infection Control Programs in Nursing Homes”).

## Infection and Functional Assessment

Traditionally, infectious disease has been studied, reported, and analyzed by determining the population at risk, attack rate, etiological pathogens, clinical symptoms and signs, laboratory findings, antimicrobial therapy, clinical and/or microbiological response (cures), and mortality. However, this approach for infections in older adults fails to adequately describe the predisposition, clinical manifestations, and outcomes of this population. Evaluation of functional ability or capacity of elderly persons is a central theme in geriatric medicine. Functional status and its role as a risk factor for infection and modifier of clinical features of infection as well as impacting clinical outcomes have been infrequently studied in geriatric patients (24).

Hopefully, in the future, clinical studies will focus on the role of functional status and disability on the pathogenesis, management, and prevention of infectious diseases in the elderly population. Functional assessment is especially important for the most vulnerable and frail older adults (i.e., those residing in long-term care facilities such as a nursing home) (25).

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# Factors Predisposing to Infection

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## Key Points

- In the old, age-related changes in host defenses play a key role in the increased susceptibility and severity of infections.
- Comorbidities are common in older persons and may further compromise host defenses.
- Innate and adaptive immunity are now known to be interactive systems; both are affected by age and disease, and changes in innate immunity affects adaptive immunity.
- Recent studies suggest that Toll-like receptors appear to be affected by age and that these changes may affect antigen presentation and optimal T-cell function.
- Age-related changes in B-cell function and in B-cell and T-cell interaction result in diminished antigen-specific antibody production.

It is well established that, when an infection occurs, the elderly are both at an increased risk for acquiring many types of infections and for increased severity of illness (1). Predisposing factors, which in part account for infection, include decrements in host defenses with age that are made worse by chronic disease, undernutrition, and certain medications that are commonly prescribed to older persons. Some of these factors are organ specific. For example, the increased prevalence of urinary tract infection in the elderly is due in part to age-related changes in the urinary tract, which include anatomic changes (e.g., prostatic hypertrophy) and altered physiology (e.g., increased bladder residual volume). Furthermore, the elderly are more likely to be hospitalized, to undergo invasive procedures, and to suffer procedure-associated complications that compromise mucocutaneous and other barriers to infection. Moreover, hospitalization and chronic illness increase the risk of colonization and subsequent infection with virulent nosocomial flora (2).

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This chapter further identifies and summarizes factors that increase the risk of infection in elderly persons. Fever, as a host defense, is not covered here because it is discussed in detail in chapter “Clinical Features of Infection.”

## **Infection Risk**

The risk for developing an infection, and to some extent its severity, is directly proportional to the inoculum and virulence of the pathogen(s) and inversely proportional to the integrity of the host defenses. Aging and comorbidities associated with aging affect all three of these factors. It is the interplay of these three variables that account for the increased susceptibility to and severity of infections in the geriatric population.

## ***Virulence***

The virulence of a pathogen is dependent on its ability to attach to and to penetrate the host and its ability to successfully replicate in the host environment. Virulence factors are properties that enable a pathogen to establish itself in the host and cause disease (3). For example, for certain uropathogenic strains of *Escherichia coli*, virulence is determined by the presence of P fimbriae, which are surface structures known as adhesins. Adhesins attach to receptors on uroepithelial cells and facilitate attachment to and colonization of uroepithelial cells. The molecular details of how P fimbriae attach to uroepithelial cells have been extensively reviewed and will not be discussed further here (4). Virulence is also dependent on the pathogen’s ability to avoid being overwhelmed by the host’s defenses and its ability to damage the host. In the case of *Streptococcus pneumoniae*, a common pneumonia pathogen in elderly persons, virulence is determined by pneumococcal capsular polysaccharide, which allows the bacterium to resist phagocytosis by host cells. This virulence factor is overcome if capsular-specific antibodies are present to facilitate opsonization.

The elderly are more likely to be colonized with virulent bacteria, especially those elderly who are exposed to nosocomial flora and who have major breaches in barriers to infection (e.g., presence of an indwelling bladder catheter, intravenous catheter, or endotracheal tube). Furthermore, for reasons that are unclear, the risk for colonization of the oropharynx by potentially virulent gram-negative bacilli or *Staphylococcus aureus* is increased in elderly patients, and this risk increases with increasing dependence and acuity of illness (2). Therefore, hospitalized elderly are at greatest risk for oropharyngeal colonization with these pathogens. Drying of upper airway secretions with age, exposure to antibiotics, and changes in local immunity may all be contributing factors for oropharyngeal colonization.

Resistance of bacteria to antibiotics, although technically not a virulence factor, potentially increases morbidity and mortality related to infections. Frail, institutionalized elderly may suffer repeated hospitalizations and undernutrition as well as undergoing repeated courses of antimicrobial therapy. Normal bacterial flora may be altered in these cases and will increase the risk for colonization by resistant bacteria.

### *Inoculum*

The inoculum is an important determinant of risk of infection and plays a significant role in the increased risk of infection in the elderly. For example, a classic study of aspiration revealed that 45% of even young, healthy individuals aspirate small amounts of oropharyngeal secretions during deep sleep (5). However, older persons are more likely to have neurovascular disease with resultant swallowing disorders and are also at more risk to undergo tube feedings, both of which dramatically increase the risk of aspiration of copious amounts of oral secretions. Furthermore, in this population, the adverse effects of alcohol, long-acting benzodiazepines, and other sedating agents further increase the risk for aspiration. Given the loss or alteration with age of important pulmonary host defenses, including cough reflex, mucociliary clearance, and changes in immune function it is not surprising that geriatric patients have a markedly higher incidence of pneumonia. Endotracheal intubation and prolonged mechanical ventilation further compromise host defenses; these interventions increase the risk of aspiration of large inocula of bacteria. Such macro aspiration dramatically raises the probability for the development of severe respiratory infection. Finally, the elderly are more likely to undergo intravascular catheterization and the placement of chronic dwelling bladder catheters. These catheters, even when meticulously maintained, serve as a conduit for inocula of bacteria, thus bypassing basic host barriers to infection.

### *Host Defenses*

Host defenses can be separated into two major divisions: nonspecific (innate or natural) and specific (adaptive or acquired) defenses. Nonspecific defenses include mucocutaneous barriers, complement, and certain effector cells such as macrophages, neutrophils, and natural killer (NK) cells. The components of the innate system remain constant over time. Specific immune defenses involve T and B cells, and these adapt and change upon exposure to various pathogens. In recent years, it has become apparent that the division of the two components of the immune response is somewhat arbitrary, because components of the innate immune system interact with components of the specific immune system to optimize the specific immune response. For example, as discussed below, dendritic cells act as antigen processing and presenting cells necessary for optimal T cell responses.

## Mucosal Defenses

Mucocutaneous tissues are more than simple mechanical barriers. The skin has antibacterial properties including a relatively low pH and glandular secretions, which have an antibacterial effect. Aging results in significant changes such as loss of dermal thickness and subcutaneous tissue as well as reduced glandular secretion, which makes the skin less capable of withstanding shearing forces. Furthermore, with age, the skin become relatively avascular, and, along with increased risk of dermoepidermal separation, increases the susceptibility to injury. Also, there is a loss of as much as 50% of Langerhans cells, the cell population responsible for immunosurveillance in the skin. Cytokine dysregulation occurs, both of which decrease the specific immune response (6). Loss of mobility resulting from coexisting diseases may lead to increased pressure and shearing forces. Edema and vascular diseases may further compromise the integrity of this important barrier and can facilitate colonization and invasion with virulent bacteria.

The mucosal host defense system, like the skin, is a first-line defense against invading pathogens. Mucus secretions and ciliary action continuously trap and remove bacteria, thus preventing microbes from gaining access to deeper, normally sterile tissues. Furthermore, the mucosal immune system contains key cellular effectors of the innate immune system discussed below (7). Immunoglobulin (Ig) A antibody is the predominant immunoglobulin of the mucosal immune system and does not appear to be significantly reduced with age. However, it is not clear whether or not aging reduces the ability of the mucosa to perform as a host defense. Nevertheless, xerostomia from all causes, periodontal disease, and certain gastrointestinal disorders such as diverticulitis and ischemic bowel disease, occur commonly in geriatric patients and potentially damage mucosal defenses.

## Effector Cells of the Immune Response

As mentioned above, the immune response is made up of two interdependent entities; these are the various components of nonspecific or innate immunity (e.g., neutrophils, macrophages, NK cells, and complement mentioned earlier) and specific immune responses (cellular and humoral immunity). Innate immunity is immediate and does not require prior exposure or sensitization to a particular foreign antigen, does not discriminate between different antigens, and is not enhanced by repeated exposure to a particular antigen. In contrast, the specific immune response is usually initiated by a specific foreign antigen and involves cells of lymphoid lineage including T cells (cellular immunity) and B cells (humoral immunity). Stimulus from a foreign antigen results in the generation of specific molecules, which, in effect, modulate responses among the effector cells of the immune response. Repeated exposure to the specific antigen enhances the immune response, which is the basis of what is an essential host defense against a wide variety of microbial pathogens. It should be mentioned that NK cells are presumably of lymphoid lineage and are an important host defense against tumor cells; they may also have some role in the defense to virus-infected cells. However, NK cells

do not require prior sensitization to become cytotoxic and are considered to be an effector cell of innate immunity. Again, innate immune system signaling is required for optimization of critical components of the adaptive immune response (8, 9). The recent exciting discovery of at least 10 distinct Toll-like receptors (TLR) created another opportunity to study the effect of aging on immune function. TLR belong to a class of molecules known as “pattern recognition receptors” and reside on the surface of various innate effector cells. TLR recognize a variety of pathogen-associated molecules, and the function of TLR is to rapidly initiate a protective response and to signal effector cells of the specific immune response to the presence of invading pathogens (10).

A summary of the specific immune response is as follows: T cells have been extensively studied in animal models and humans including aging populations. Activated T cells are composed of two distinct cell types: T helper cells (involved in the defense against extra cellular pathogens and express the CD4 marker (CD4+)) and cytotoxic T cells (involved in the defense against intracellular pathogens and express the CD8 marker (CD8+)). T helper cells that are undifferentiated are called Th0. Th0 can then differentiate into Th1 or Th2. Th1 and Th2 have been extensively studied. Th1 cells secrete interleukin 2 (IL-2), tumor necrosis factor-beta (TNF- $\beta$ ), and gamma interferon. Th1 cells promote antibody production and also enhance immune defenses against intracellular bacterial and protozoan pathogens. Th2 cells secrete interleukins 4, 5, 6, 9, 10, and 13 and enhance immune defenses against intestinal and multicellular pathogens in part by enhancing IgE antibody production and stimulating eosinophils. CD8+ T cells have the ability to lyse cells infected with intracellular pathogens including viruses (11–14).

T cells that have not yet responded to a specific antigen are referred to as naive T cells that express the marker CD45RA and are relatively short lived. T cells that, after clonal expansion and differentiation, have a T-cell receptor (TCR) with high avidity for antigen may become short-lived effector cells or long-lived memory cells. Memory T cells express the marker CD45RO and are more easily and rapidly activated than naïve T cells.

Each mature T cell has a unique receptor that is specific for a certain antigen (epitope), and the total T-cell population provides an extensive capacity to bind with a multitude of different antigens. The TCR does not bind directly to antigen but requires processing of the antigen by antigen-presenting cells (APC). After taking up antigen, APCs (macrophages, dendritic cells, and others) break the antigen into polypeptide components, which are complexed on the cell’s surface with molecules that are loaded within the major histocompatibility complex (MHC) class I or II molecules. APCs typically express MHC class II molecules that are necessary for CD4+ (helper) T-cell activation, and APCs migrate into lymphoid tissues to facilitate communication with naïve T cells (11–13).

The TCR in concert with another T-cell marker, CD3 (expressed on all T cells), after antigen recognition and engaging costimulatory molecules, forms the TCR-CD3 complex, which can then initiate the complex cascade of signal transduction resulting in cytokine secretion, clonal expansion, and differentiation of T cells necessary for the specific T-cell response. Activated T cells then may migrate into other tissues and interact with B cells (11–14).

## *Changes with Age*

The data on immune function changes with age are less compelling in humans as compared with animal models, especially when experiments utilize SENIEUR protocols that minimize the effects of disease and medication and exclude the majority of older subjects (15). The components of innate immunity (e.g., phagocytosis by macrophages, neutrophils, complement activity, and NK activity) in the past did not appear to be greatly affected by aging in healthy elderly patients. However, more recent data suggest macrophage function may be altered with age; a recent review of the effect of age on human monocyte TLR concluded that aging effects TLR signaling resulting in both diminished cytokine production and costimulatory molecule production necessary for optimal T-cell function (10). This aging effect was based on experiments demonstrating that stimulating TLR 1/2 on monocytes obtained from older adults produced 50% less TNF- $\alpha$  and IL-6. TLR1, and TLR2 are critical receptors because they recognize lipopeptides present in the cell walls of a variety of gram-negative and gram-positive bacteria. Further experiments demonstrated monocytes from older persons after influenza vaccination showed reduced expression of CD80 and CD86 costimulatory proteins that are important for optimal T-cell activation and vaccine response (16). Finally, NK cells appear to increase with increasing age but the response of NK cells to cytokine signals may be altered with healthy aging (17), and recent reviews of ageing effects on NK activity conclude that there appears to be diminished proliferative and cytotoxic activity of NK cells with age (8, 18).

The state of one's health, exercise, and nutritional status will influence measures of specific immunity; however, with age, there are consistent changes observed in the cellular and humoral components of specific immunity. First, it is firmly established that with age there is a shift from naive T cells to memory T cells and that both T-cell proliferation and IL-2 production are reduced (15, 18, 19). Although, in some studies IL-6 has been found to be increased with age, independent of disease or medication, but this is not a consistent finding. One study did find that elderly caregivers had increased levels of IL-6 during periods of stress (20), and a more recent study demonstrated increasing levels of IL-6 with increasing levels of frailty (21). Other studies have demonstrated alterations in cytokine production and increased cytokine dysregulation with age (22). T-cell proliferation in response to mitogens and specific antigens is decreased with aging and is not explained entirely by reductions in IL-2 production (18). Studies consistently demonstrate reduced T-cell proliferation with age, but there is wide inter individual and population variability. Finally, B-cell production of specific, high-affinity antibodies is reduced with age. This is not only an *in vitro* observation because, as a population, even relatively healthy elderly persons do not mount as great an antibody response to T-cell-dependent antigens such as influenza vaccine as compared with a younger population. It also appears that cytotoxic T-cell functions are reduced somewhat with aging. Finally, with age alterations of apoptosis (programmed cell death) have been postulated to explain some of the age-related changes in immune function (23). (Table 1 summarizes the foregoing discussion.)

**Table 1** Effect of aging on immune function

	Decrease	Increase, no change, or inconclusive
<b>T cells</b>		
T-cell number		X
Thymus gland	X (involutes)	
Memory T cells		X (increased)
Naive T cells	X	
DTH <sup>a</sup>	X	
Cytotoxicity	X	
Proliferation	X	
Interleukin 2	X	
Interleukin 4		X
Interleukin 6		X (probably increased) <sup>b</sup>
Interleukin 10		X
Interferon-gamma		X
<b>B cells</b>		
B-cell number		X (increased)
Proliferation	X	
High-affinity antibody production	X	
Nonspecific antibody production		X (increased)
Autoantibody production		X (increased)
<b>Macrophages</b>		
TLR <sup>c</sup> function	X	
<b>NK<sup>d</sup> cells</b>		
Cytotoxicity	X	

<sup>a</sup>Delayed type hypersensitivity reaction

<sup>b</sup>See section “Host Defenses”

<sup>c</sup>Toll-like receptor

<sup>d</sup>Natural killer

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# Clinical Features of Infection

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## Key Points

- Clinical symptoms and signs of infection in older persons may be less apparent or even absent.
- Types of infections are dependent both on the clinical setting and the functional status of older persons; the pathogens involved in common infections are often different for the old compared with the young.
- Fever, the “cardinal sign” of infection, has a protective effect in limiting infection in experimental models, but this important indicator of infection may be blunted or absent in older persons.
- On average, older persons as compared with younger persons have lower baseline temperatures; a significant change in temperature (1.1°C or 2°F or more) from baseline may indicate the presence of an infection in older persons.
- Similar to younger persons, fever of unknown origin in older persons is usually due to infection; however, non-infectious inflammatory conditions and neoplasms account for a higher percentage of cases in the old compared with the young.

## Overview

Infections in older persons often present in an atypical, nonclassical fashion that creates unique diagnostic challenges to clinicians. Furthermore, the differential diagnosis of infectious diseases in the old differs from the young because, it is dependent on both the clinical setting and the patient’s underlying functional status. For example, “free living,” independent, healthy older persons are prone

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to respiratory infections such as influenza, bronchitis, and bacterial pneumonia; genitourinary infections and intraabdominal infections, including cholecystitis, diverticulitis, appendicitis, and intraabdominal abscesses also occur. However, institutionalized elderly are more likely to develop aspiration pneumonia, urinary tract infection, (especially if a chronic indwelling bladder catheter is present), and skin and soft-tissue infections. Infections in the old also differ from the young because, in this age group, infections are often caused by a more diverse group of pathogens. This difference is best exemplified by urinary tract infection, which in the young occurs almost exclusively in females and is usually caused by *Escherichia coli*. In the aged, a variety of gram-positive cocci and gram-negative bacilli, sometimes in combination, are potential pathogens for a urinary tract infection, and at least a third of urinary tract infections occur in males. This diversity of pathogens is the reason that obtaining a urine culture prior to empirical therapy for symptomatic urinary tract infection is recommended for older persons. Similarly, pneumonia in the young is usually due to relatively few pathogens such as *Streptococcus pneumoniae* and *Mycoplasma pneumoniae*. Yet, a small but significant number of cases of community-acquired pneumonia in older persons are caused by gram-negative bacilli in addition to *S. pneumoniae* (1–3).

Morbidity and mortality rates for infections are usually higher in the elderly as compared with the young (4). These observed higher mortality and morbidity rates are due in part to factors such as (1) lower physiologic reserve capacity due to biologic changes with age and comorbidities, (2) age and disease-related decrements in host defenses, (3) chronic illness, and (4) higher risk for adverse drug reactions due to multiple medications and age-related physiologic changes that alter the pharmacokinetics and pharmacodynamics of many medications. Additional contributing factors include a greater risk for hospitalization, and, therefore, exposure to nosocomial pathogens, a greater risk of undergoing invasive procedures, and increased likelihood of suffering a procedure-associated complication. Finally, delay in diagnosis and the initiation of appropriate empirical antimicrobial therapy is an important contributing factor. Diagnostic delays may commonly occur in the elderly population, and this group is the one who can least tolerate such delays. However, since infections in older persons commonly present in an atypical or nonclassical manner, early diagnosis may be difficult. Thus, infections in this age group provide a unique challenge to clinicians.

## **Clinical Manifestation of Illness**

Atypical or nonspecific clinical manifestations due to infection are commonly observed in older adults and recently have been reviewed extensively (5). Listed in Table 1 are some of these symptoms and signs and also nonclassical presenting features. Delirium, agitation, confusion, lethargy, anorexia, falls, abnormal movements, focal neurologic signs, and urinary incontinence may all be the sole symptom observed at initial presentation of any infection in older adults. Furthermore, bacteremia may occur in the absence of fever and present with dyspnea, confusion, and/or hypotension.

**Table 1** Altered presentations of infection in the elderly

Potential findings with any infection	Potential findings (or lack thereof) with specific infections
Change in cognition (e.g., Delirium)\nAgitation)	Bacteremia
Falls	Dyspnea, confusion, falls, hypotension May be afebrile
Lethargy	Pneumonia
Anorexia	Tachypnea
Failure to thrive	May be afebrile
Change in baseline body temperature	Cough and sputum production may be absent
	Intraabdominal infection
	Anorexia
	May be afebrile
	Peritoneal signs may be absent
	Meningitis
	Confusion, altered consciousness
	Stiff neck may be absent
	Tuberculosis
	Weight loss, lethargy
	Failure to thrive
	May be afebrile
	Urinary Tract Infection
	May occur without dysuria, frequency, flank pain or fever

In geriatric patients with bacterial meningitis, the classical finding of a stiff neck may be absent, and the older patient with pneumonia may not have cough, sputum production, or fever, whereby the only sign alerting the clinician of a pneumonia may be tachypnea (6, 7). Peritoneal findings may be absent in elderly patients with intraabdominal infection (8, 9) or symptomatic urinary tract infection may, at times, present solely as a decline in cognitive function but without dysuria, urgency, or frequency. The severity of clinical manifestations of infectious diseases in older adults may not be in proportion to severity of the underlying infection. In one classic study, a high percentage of older women presenting with symptoms and signs of pyelonephritis indistinguishable from those of younger women were bacteremic, whereas none of the younger women studied had positive blood cultures (10). In more recent studies, it was confirmed that costovertebral angle (CVA) tenderness may be not be present in older persons with pylenephritis (11). In summary, virtually any change in functional status in the elderly may be an indication of the presence of an acute illness that often is an infection. Furthermore, there may be a dissociation of clinical findings with severity of illness.

## Fever in the Elderly

Classical studies of bacteremia (10, 12), and with few exceptions studies of pneumonia (7, 13–15), endocarditis (16–18), nosocomial febrile illness (19), meningitis (20), intraabdominal infection (21), and tuberculosis (22) demonstrate both that a higher percentage of older persons as compared with younger persons demonstrated a blunted fever response; further, up to one third of older patients with serious bacterial or viral infections do not mount a robust febrile response (23). This mitigated fever response is further confirmed by a study of acute intraabdominal infection in octogenarians in whom a large percentage with acute cholecystitis, intestinal perforation, and appendicitis presented with temperatures less than 37.5°C (21). Additionally, a study of nosocomial febrile illness in a geriatric medicine unit showed that the mean “febrile” rectal temperature of elderly subjects reached only 38.1°C (100.6°F). In this study, only 8% of febrile patients had rectal temperatures greater than 38.5°C (101.3°F) (19). Taken together, the significance of these findings is that although fever is the cardinal sign of infection its absence in elderly patients is not uncommon and may delay diagnosis and the initiation of appropriate antimicrobial therapy.

Not only is the presence of fever the single most important diagnostic feature of infection, but a febrile response or its lack thereof also has other important implications. Weinstein and colleagues (24) demonstrated in their classic review of several hundred cases of bacteremia and fungemia that the more robust the fever response to these serious infections, the more likely was there survival in the patient. For many infectious disease, this and other studies have firmly established that the absence of fever in response to a serious acute infection is a poor prognostic sign for all age groups. Although the diagnostic and prognostic implications of fever are clear, it is less well established that in humans fever is an important host defense mechanism..

Animal models provide the best evidence that fever is an important host defense mechanism. Experiments showed that poikilothermic animals, in response to infection, move to warmer environments in order to raise body temperatures; this behavior has an impact on survival. For example, in one classic experiment, a species of lizards was placed in terrariums that were kept at different temperatures. The body temperatures of these poikilothermic animals equilibrated with the environmental temperature of the terrarium in which they were housed. Subsequently, the animals were infected; as a result of this infection, those kept in the higher temperature terrariums (thus having higher body temperatures) had a much better chance of survival than those animals kept at lower temperatures (25). Similar findings were demonstrated in goldfish (26). Based on these and other animal data, including additional data generated from mammalian experiments, fever may be inferred as an important host defense mechanism in humans. The mechanism(s) by which fever may enhance host defenses is not due to a direct effect of physiologically achievable temperature elevations inhibiting most pathogens. The exceptions are *Treponema pallidum*, the gonococcus, and certain strains of *Streptococcus pneumoniae*. In these cases, normal physiologically achievable body temperatures in humans can inhibit bacterial growth directly. These exceptions aside, experimental data suggest that normal physiologically achievable elevations in body

temperature enhance the production of monokines, cytokines, and other factors (interleukin 1, interleukin 6, and tumor necrosis factor). These factors are also endogenous pyrogens, and they appear to facilitate the adherence of granulocytes and other effector cells of the immune response to endothelial cells. They also promote immune effector cell migration into interstitial tissue spaces that contain pockets of infection.

The reason(s) for the blunted fever response to infection that was observed in a substantial number of elderly patients has not been completely elucidated. One explanation is that the baseline body temperature is lower for this population (see discussion following); another is the inherent inaccuracies in oral temperature measurement in a subset of elderly patients with dementia, mouth breathing, and variations in respiratory patterns. Further inaccuracies in temperature measurement may be caused by the ingestion of hot and cold foods during the time of measurement. Moreover, routine rectal temperatures are often impractical in subpopulations of debilitated, poorly cooperative patients. The widespread availability of tympanic membrane thermometers may reduce such error in temperature measurement. Reasons for the blunted fever response other than lower baseline temperatures and difficulties in accurately measuring temperatures noted above have not been completely established.

For the blunted fever response in the elderly, an understanding of additional potential mechanisms may be gained by reviewing the current knowledge of the pathogenesis of fever (27–30). It is now established that bacterial products such as lipopolysaccharide bind to Toll-like receptors present on immune, endothelial, and epithelial cells and induce these cells to produce a variety of factors including endogenous pyrogens (tumor necrosis factor, interleukin-1, interleukin-6 and interferon-alpha). These pyrogens are either produced distally at the site of infection and then enter the circulation or locally by macrophages adhering to endothelium in circumventricular organs of the brain. These pyrogens then act on the anterior hypothalamus resulting in a biochemical cascade including the release of prostaglandin E2. The resulting effect is an elevation of the “hypothalamic thermostat,” which in turn results in shivering, vasoconstriction, and certain behavioral responses, all of which elevate core body temperature (28). When the infection subsides, the “thermostat” is reset back to normal whereby sweating and temperature-lowering behavior ensues, restoring body temperature to baseline. The role of cytokines in the pathogenesis of the early fever response has been challenged. This is in part because endotoxin-challenged animal models may develop fever before peripheral macrophages are able to produce cytokines. It is possible that endotoxin may act directly on the vascular endothelium of the anterior hypothalamus or may excite hepatic vagal afferents which signal the preoptic area of the hypothalamus (31, 32).

It is possible that these pathways could be affected by aging, and thermoregulation in the elderly appears to be impaired to some degree. This is evidenced by the increased morbidity and mortality in older persons from heat stroke and hypothermia. Animal data suggest an impaired response to endogenous pyrogens with normal aging (33–35) as well as diminished production of these pyrogens with age (36). Evidence from one model suggests that the aging brain may respond normally

to directly injected endogenous pyrogens, implying that there may be a defect in endogenous pyrogens crossing the blood-brain barrier (37). Intracerebroventricular injection of interleukin 1 showed identical immediate fever responses in both young and old rats, suggesting an inability of peripheral endogenous mediators to reach the central nervous system rather than an unresponsiveness of the central nervous system (38); others demonstrated diminished production of endogenous pyrogens with age in various rodent models (36). Finally, rodent experiments have suggested that changes in thermogenic brown fat may play a role in the blunted fever response of aging (39). Thus, reduced production and response to endogenous pyrogens may be important in the pathogenesis of the blunted febrile response to infection observed in older persons. Given the most recent data, it is clear that aging may affect Toll-like receptor function (40) and result in diminished endogenous pyrogen production and may also alter any of the efferent pathways involved in the fever response.

## **Baseline Temperature, Significance of Fever, and FUO**

The normal and febrile body temperature for older adults has been reviewed (23). In summary, it has been known for some time that baseline temperature declines significantly in the old. The clinician can remember this fact by remembering the statement “the older, the colder.” Lower baseline temperatures, at least for debilitated elderly, has been reaffirmed by Castle and co-workers (41, 42), who demonstrated that baseline temperature was decreased among nursing facility residents. Castle and colleagues’ studies further demonstrated that infections often led to “robust” or normal increases in body temperature from baseline. However, because the baseline temperature was lower, the rise in temperature, which accompanied infection, often did not reach an oral temperature of 101°F (38.3°C). Generally, 101°F (38.3°C) is the temperature level that many clinicians consider to be the definition of fever. These studies suggest that new definitions for a fever need to be established for the geriatric patient. Based on these studies, an oral temperature of 99°F (37.2°C) or greater on repeated measurements in an elderly nursing facility resident with a change in clinical status should be considered a fever. In addition, a persistent rectal temperature of 99.5°F (37.5°C) would constitute a fever as would an elevation of baseline body temperature of 2°F (1.1°C) for patients in this setting. These findings contributed to the recommendation by the Practice Guidelines Committee of the Infectious Diseases Society of America that a clinical evaluation be done for nursing home residents exhibiting a change in clinical status associated with a single oral temperature over 100°F (37.8°C) or persistent oral or rectal temperature over 99°F (37.2°C) or greater than 99.5° (37.5°C) respectively. Two or more readings of greater than 2°F (1.1°C) over baseline regardless of site of measurement should also stimulate an evaluation for infection (43). If, on the one hand, other symptoms and signs of infection exist, the probability of an infection is further increased; on the other hand, in some cases, a significant decrease in body

temperature (hypothermia) indicates the presence of a serious infection that is complicated by bacteremia. Finally, the clinician should always remember that any unexplained acute or subacute change in functional status, regardless of whether or not a fever or change in body temperature is present, may indicate the presence of an infection.

The presence of a “robust” or normal fever response to infection in an elderly person has special significance. An extensive study of over 1,200 ambulatory patients showed that in contrast to younger patients in whom “benign” viral infections were common, the older febrile patient is more likely to harbor a serious bacterial infection (44). This finding was verified by an additional study, which also confirmed that leukocyte elevations in response to an infection were less common in the aged compared with the young (45). The presence of an elevated white blood count or a “left shift” to more immature neutrophils is more likely due to serious infection in the older population (45, 46). Based on these studies, it is recommended that any elderly patient with an oral temperature of 101°F (38.3°C) or greater be evaluated for a serious bacterial infection.

Fever of unknown origin (FUO) in older persons differs from fever in the young because the etiology is different. Although infections are the leading cause of FUO in both old and younger persons, in the old, non-infectious inflammatory diseases and neoplasms account for a high percentage of FUO cases. Moreover, a diagnosis can be made in a higher percentage of cases of FUO in older patients. Finally, it is well worthwhile investigating FUO in the old, because treatable conditions are often found (47–50).

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# Role and Importance of Functional Assessment in Infections

Robert M. Palmer

## Key Points

- Functional assessment identifies older patients with infections who are at risk for functional decline, it provides clues that infection is worsening, and it predicts outcomes of mortality and discharge location.
- Clinical trials that included elderly patients with infections show that functional assessment, when combined with multifactorial interventions, prevents functional decline in hospitalized patients.
- Delirium is a common complication of infections and is predictable, recognizable, and potentially preventable.
- Validated screening tools and scales facilitate the assessment of physical and cognitive functioning of older patients.
- As physical functioning is vital to the quality of life of older patients, and, for all older patients with infections, a brief functional assessment is recommended.

While functional impairment before the infection (baseline) is associated with a higher likelihood of incident infection, infections in elderly patients are associated with an increased risk of subsequent functional decline and a loss of self-care ability (1). Elderly patients are more vulnerable to functional decline with infections due to the following: (a) diminishing homeostatic reserves with aging, (b) comorbidities that are exacerbated by infection, (c) polypharmacy with the risk of adverse drug interactions and adverse effects, (d) and the nonspecific presentation of illness that delays accurate diagnosis and treatment of the infection. This chapter provides an overview of the important role of functional assessment in older patients with an infectious disease; it highlights the relationship between infection and functional status, and it offers guidelines for performing a functional assessment with the potential to impact the patient's response to therapy.

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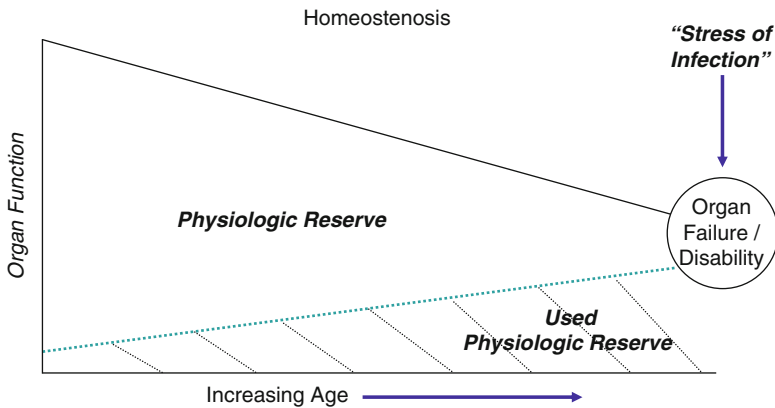
## The Importance of Functional Status in Older Patients

Functional status is typically defined in terms of activities of daily living (ADL), basic and instrumental (BADL and IADL, respectively). BADL includes the ability to independently bathe, dress, groom, eat, move from bed to chair (transfer), toilet and maintain continence. The more complex IADL tasks include the following: the ability to independently take medications, handle finances, perform household chores (cooking, laundry), shop, use public transportation, and use a telephone (1). The ability to perform the ADL without personal assistance has clinical and social ramifications. Patients who cannot perform their BADL are generally not safe to live alone. Patients who are dependent in the performance of IADL are more likely to lose physical functioning during the course of hospitalization for an acute illness. Functional status has prognostic importance that is not always captured by measures of disease severity, comorbidity, or diagnosis. In studies of hospitalized elderly patients, many of who are admitted for treatment of infections, dependence on the performance of BADL is an independent predictor of mortality, length of stay in hospital, placement in a nursing home, and costs of medical care (2, 3). Among hospitalized patients, nosocomial infection and severe functional impairment are stronger predictors of mortality than is age (4); among nursing home residents, baseline performance of BADL is the major determinant of survival after pneumonia (5).

The impact of functional status, both in its influence on outcomes and in its consequence of infection, is illustrated in studies of elderly patients in long-term care facilities. A study of 1,324 residents aged 65 and older (mean age 85.7; 76.6% female) in 39 nursing homes in Switzerland examined functional decline defined as death or decreased function (ADL) at follow-up and functional status score using a standardized measure. At the end of 3–6 months of follow-up, residents with infection had higher odds of functional decline, even after adjustment for baseline characteristics and occurrence of a new illness (6). This study of nursing home residents (6) suggests that with lower ADL function there is a greater risk for subsequent infection, and those who become infected are at greater risk for further functional decline. Thus in a vulnerable population functional impairment may predispose to infections as part of a downward spiral, and, in turn, infections may further accelerate functional decline (6). In another study, 116 nursing home residents who developed an influenza-like illness as compared to 127 randomly selected resident controls without an influenza-like illness were significantly more likely (25%) than control subjects (16%) to experience a decline in functional status (7). In a study of 781 episodes of lower respiratory tract infection among 1,044 residents of long-term care facilities, the incidence of decline in functional status was 29% (8). Residents who had a decline in functional status at 30 days from the time of lower respiratory tract infection were less likely to recover to their baseline status at 90 days. In residents with lower respiratory tract infections, ADL status is a predictor of 30-day mortality (9).

## Pathophysiology of Functional Decline with Infections

Acute or chronic infections can adversely affect the functional status of elderly patients, especially those with multiple comorbid conditions and high severity of illness. The process of aging depletes an individual’s homeostatic reserve and the capacity of organ systems to adapt to physiologic stressors or “homeostenosis” (Fig. 1). Redundancy in physiological systems, abundant in youth, declines steadily over time. Consequently, the impact of a single acute illness or event affects the aging individual to a greater degree than a younger individual by both its effect on multiple organ systems and its duration. An infection, such as influenza, that might cause minor symptoms in a young person can overwhelm the homeostatic reserve of an elderly patient and lead to multiple organ system dysfunction (for example, brain, kidney, heart, and liver dysfunction). The clinical expression of organ system failure is that of “functional decline” (a delirious, profoundly weak patient unable to eat, bathe, or transfer independently). The loss of homeostatic reserve also diminishes the older individual’s ability to recover from such an acute illness. The older the patient the longer it takes to regain independence in the performance of BADL. The older patient’s loss of reserve after an acute illness causes a cascade of functional decline in physical functioning that predisposes the patient to further decline and complications resulting from the illness itself or from its intended therapy. The impact of infection on functional status is further confounded by aging-related changes in immunity, increasing numbers of comorbid conditions with aging, greater prevalence of impairment in mobility, prevalent nutritional deficiencies including protein-calorie malnutrition, frequent exposure to ill (infected) individuals (nosocomial infections), and exposure to multiple antibiotics with risks of adverse effects, and instrumentation.



**Fig. 1** “Homeostenosis”: the pathophysiology of diminishing functional reserve leading to organ failure and functional disability in patients with infection

Physiological effects of infections can exacerbate the dysfunction of organ systems, leading to the loss of the patient's independent physical functioning. For example, pathogens in pneumonia diminish respiratory function; bacterial infections of the heart can diminish cardiac output resulting in the patient's loss of ability to walk due to breathlessness or the patient's loss of ability to conduct daily activities due to generalized weakness. Infections can also produce broader effects: Influenza, beyond its typical respiratory involvement, has been shown to be directly damaging to muscle tissue (10). In one study, gram-negative sepsis led to self-perceived and measurable declines in the ability to work and perform ADL (11). Specific diseases such as chronic obstructive pulmonary disease, congestive heart failure, and dementia affect both the respective organ system and the presentation of and response to the treatment of an acute infection. Functional limitations associated with chronic diseases (e.g., oropharyngeal dysphagia, reduced cough reflex) place the patient at risk for infections. These patients are also being offered a growing number of surgical procedures and are exposed to instrumentation with prosthetic devices (e.g., implantable cardiac devices, artificial joints) and broad-spectrum antibiotics. Consequently, the chronically ill elderly patient is placed at increased risk for aspiration pneumonia, *Clostridium difficile* colitis, recurrent urinary tract infection, and infection of prosthetic devices. Once again, the interaction of these chronic diseases, infections, and homeostatic failure result in the phenotype of a physically frail appearing patient with generalized weakness, malnutrition, and loss of self-care ability.

## **Nonspecific Presentation of Infection**

In older patients, early symptoms of infections are often nonspecific (see also Chapter "Clinical Features of Infection"). The nonspecific manifestations of infections are attributable to the complex interaction of aging, the loss of homeostatic reserve, the severity of illness, and the impact of comorbidities. For example, an older patient with community-acquired pneumonia and prevalent but stable heart failure associated with diastolic dysfunction (commonly seen with aging) is admitted to the hospital with a fall, dehydration and renal insufficiency, severe dyspnea, and acute confusion. The pneumonia (plus fever, tachycardia, and hypoxemia) precipitated an exacerbation of heart failure and impaired renal function thereby contributing to dehydration. Beyond specific organ symptoms due to infection, general nonspecific symptoms such as malaise, weakness, anorexia, and subsequent malnutrition arise and further increase the impact of the infection on the patient. Symptoms and signs of infectious diseases may differ in older compared with younger adult patients; presenting symptoms often being altered, blunted, or absent. For example, fever and leukocytosis, identifiable hallmarks of acute infection, may be absent in an elderly individual. Worsening physical or cognitive functioning might indicate

that the underlying infection is not responding to antibiotics as might occur in antibiotic-resistant infection.

Nonspecific symptoms can also provide clues to the presence of underlying infection. Delirium is a common complication of infection in older patients (11). Commonly, a change in cognition with features of delirium is the first or dominant symptom of an acute infection such as pneumonia or urinary tract infection (12). Indeed, any older patient with the sudden onset of symptoms of delirium should be considered to have an infection even if the patient is afebrile and without symptoms that are referable to a specific organ system. The occurrence of delirium is a “red flag” that the patient’s condition is deteriorating and underscores the need for an extensive search for additional predisposing or precipitating causes. For example, the patient with pneumonia might also have hypoxemia, dehydration, or fever, conditions that exacerbate the cognitive symptoms of delirium.

Infections can have a dramatic impact on physical functioning. For example, sudden weakness or paresis of the lower extremities provides a clue to the presence of a paravertebral or epidural abscess. An accidental fall can be the first symptom of bacteremia due to lung or urinary tract infections. Chronic or subacute infections can present with nonspecific effects on functional symptoms as well. Endocarditis can present very insidiously as otherwise unexplained weight loss. In mycobacterial infections, weight loss, apathy, and malaise can be the dominant symptoms. The presence of comorbidities such as lymphoma can obscure the diagnosis of an insidious infection as the nonspecific features of fever and fatigue are attributed to the cancer. Many “atypical” symptoms often go unnoticed because they were not considered or are attributed to normal aging (e.g., memory impairment) thereby delaying diagnosis and exacerbating the infection’s impact on the patient’s health and subsequent functional status.

Even common symptoms of infectious diseases can affect daily activities and lead to a vicious cycle of functional decline and worsening infection. For example, fever, anorexia, malaise, diarrhea, and headache impair the ability to feed one’s self, ambulate, perform daily chores, drive and consequently result in dehydration, malnutrition, immobilization, and social isolation. A cascade of decline results and predisposes the patient to falls, delirium, incontinence, iatrogenic illness, and loss of independent living. In turn, this cascade of functional decline increases the probability of recurrent infection and the risk of mortality.

Adverse effects of medications can produce nonspecific symptoms associated with declines in self-care. Medications that are given for appropriate indications (e.g., diverticulitis and urinary tract infections) can be problematic in elderly patients angiotensin-converting enzyme inhibitors, beta blockers, high-dose statins, platelet inhibitors, and some antibiotics used for treating diverticulitis, increase the potential of adverse interactions with other medications. Common adverse effects to specific agents include sedation, confusion, dry mouth, and anorexia, which in turn can lead to cognitive impairment, undernutrition, immobility, and deconditioning, and falls.

## **Functional Assessment**

The functional assessment is an integral component of a comprehensive geriatric assessment, which includes the process of identifying medical, environmental, and psychosocial factors that impact an elderly individual's functional capacity. Traditionally, a comprehensive geriatric assessment is an extensive and lengthy process, usually performed by a multidisciplinary team that can include a physician, nurse, social worker, and any combination of physical therapists, occupational therapists, speech therapists, pharmacists, or nutritionists. Comprehensive geriatric assessment is effective in identifying risk factors for functional loss, reducing the rate of functional decline in inpatient and outpatient settings, and improving quality of life (13). Assessment of physical functioning begins by cataloging the patient's chronic illnesses and the predisposing factors for decline in the ability to perform the ADL. Besides the effects of the infection the greater the number of chronic diseases identified in an individual the greater the risk of functional decline.

The assessment reviews the patient's level of independence in performing both BADL and IADL. The initial assessment establishes a benchmark for future comparisons and also acts as a guiding post for expected functional status once the acute infection is resolved, as validated in studies of acute hospitalization (14). For example, a patient who was independent in all ADL prior to the onset of community-acquired pneumonia but is now unable to transfer or walk without assistance, should return to his or her previous level of independence once the infection is resolved or shortly thereafter.

### ***Instruments and Tools***

Validated measures of physical and cognitive functioning can be employed for the evaluation of a patient with an infectious disease (Table 1). Both self-report (or proxy report) and performance-based measures are available and can be completed efficiently, often in concert with members of an interdisciplinary team. The instruments vary in their sensitivity and specificity for clinical conditions, but are still useful to detect at-risk patients or those with prevalent functional impairments.

### ***Self-Reports***

Baseline information regarding a patient's ability to perform ADL is obtained through direct questioning of the patient or an accompanying caregiver. Self-reported performances of ADL are commonly used as a surrogate marker for physical functional capacity. Capacity can be measured by determining how many of these activities the patient is capable of doing independently (that is, without another person's assistance). The Katz index of ADL and variations are common measures

**Table 1** Functional assessment: screening and monitoring of elderly patients with infections

Domain	Measure	Comment
Activities of daily living (ADL)	Query whether patient can perform without personal assistance <i>Basic ADL</i> : bathing, dressing, transferring, toileting and continence, eating	<i>Basic ADL</i> often decline during acute infection. Baseline ADL predicts ADL upon recovery. Impaired ADL increases risk of adverse outcomes from infections
Mobility	<i>Instrumental ADL</i> : handling finances, taking medications, using public transportation, performing household chores, laundry, preparing meals, using telephone Timed Up and Go test: observe patient stand up from chair, walk 10 feet, turn around, return to chair, sit down	<i>Instrumental ADL</i> dependency at baseline predicts loss of Independence in basic ADL during hospitalization High risk of falls in patients unable to complete this task within 30 s; observe for impaired gait (shuffling, poor stride length or unsteadiness)
Cognition	<i>Delirium</i> : acute onset and fluctuating course; inattention; plus either/or both disorganized thinking and altered level of consciousness Test of attention: digit span <i>Dementia</i> : History of baseline memory loss and disability due to impaired cognition. Cognitive tools: Mini-Mental State Examination (MMSE); Short Portable Mental Status Questionnaire (SPMSQ); clock draw test	Delirium is potentially preventable by intervening on predisposing factors: dehydration, hearing and visual impairments, cognitive impairment, immobility, sleep deprivation. MMSE time consuming and requires written responses; SPMSQ is shorter; does not require written response. Clock draw can be combined with 3-item recall. These tools do not distinguish dementia from other causes of cognitive impairment; they are most helpful in quantifying cognitive deficits Many depression scales are validated, but, unlike the others, the GDS has predictive validity in hospitalized elderly patients.
Depression	Short-form Geriatric Depression Scale (GDS, 15 item)	Predicts functional decline and subsequent mortality
Nutritional status	Low body mass index	Values below 19 are associated with increased risk of mortality. Laboratory findings of a low serum albumin or anemia, while not specific for malnutrition, are commonly seen with low body mass index
Social support	Primary caregiver	Primary caregiver is crucial to the transitions of care of hospitalized patients. The secondary caregivers are often supportive of the patient and the primary caregiver. The quality of caregiving often determines whether the patient lives at home or in an institutional setting



of ADL function. The Lawton and other scales are often used to measure IADL (15). As noted, a loss of ability to perform any of these ADL during the course of the infection is a marker of impending further decline and serves as a prompt for further investigation into the causes of decline and for interventions to restore independent functioning. Patients with ADL or gait impairment often benefit from physical and occupational therapies.

### ***Performance-Based Measures***

These measures of gait, balance, and mobility provide information that is complementary to self-reported ADL scales. Gait is noted after watching the patient transfer from bed to chair. Difficulty standing up even with the use of a chair's armrests implies weakness of the proximal leg or hip muscles or postural instability that can be associated with orthostatic hypotension, generalized deconditioning, or neurologic conditions such as parkinsonism. A slow, hesitant or shuffling gait is common in deconditioned or fearful patients. If this slow or shuffling gait is a new finding then further evaluation is required and steps are needed to reverse the deficits in physical functioning. For example, the patient might improve with additional fluids and calories, discontinuation of a hypotensive medication, or the addition of physical therapy and use of an assistive device. Tools that are used to measure gait and balance in research (1) are often not feasible to use in the hospital or when patients are too acutely ill. One quick measure of mobility, the Timed Up and Go (TUG) Test, is a practical tool for inpatients whom are able to walk (16). The patient is timed while rising from a chair, walking 10 feet, turning, and returning to sit in the chair. Patient's unable to complete this task or require more than 30 s are at high risk for falling. Improvement in these performance-based measures should also correlate with resolution of the underlying infection. For example, even before fever and leukocytosis resolve after antibiotic treatment for acute infection, the patient's ability to perform ADL and to complete the TUG test are evidence that the infection is resolving. In complicated infections (e.g., wound, osteomyelitis) the patient's ability to transfer to chair from bed is often the first objective finding of improved health status in an otherwise prolonged state of convalescence.

### ***Cognitive Function***

Delirium, dementia, and depression are common causes of cognitive dysfunction in elderly patients. Clinical features of delirium include disturbance of consciousness (i.e., reduced awareness of the environment) with reduced ability to focus, sustain, or shift attention; change in cognition (e.g., memory deficit, disorientation, and language disturbance) or perceptual disturbance. Common features include increased or reduced psychomotor activity, disorganized sleep-wake cycle, and fluctuation

of symptoms over the course of the day (frequently vacillating between a hyperactive and a hypoactive state). There is usually evidence from the history, physical examination, or laboratory findings that the disturbance is caused by an etiologically related general medical condition (12). The diagnosis of delirium is made by documenting the onset of an acute change in cognition with fluctuation, inattention (e.g., poor eye contact, inability to complete a digit span test), disorganized thinking or altered level of consciousness. Tests of cognition are used to confirm cognitive impairment and to quantify the type and extent of deficits. The Mini-Mental State Examination (MMSE) includes 30 items and is scored from 0 (worst) to 30 (best); it includes memory, attention, calculation, orientation, language, executive function, and visuospatial function (17). A common cutpoint for dementia is a score of 24 or less. The MMSE is time-consuming to perform and difficult for ill patients to complete, as it requires written responses; like all brief tests of cognition, the MMSE cannot distinguish delirium from other causes of cognitive impairment. The Short Portable Mental State Questionnaire (SPMSQ) has only 10 questions and does not require written responses (18). The cutpoint for dementia is three or more errors. A clock draw test is a commonly used cognitive screen: the patient is asked to draw a clock and place the hands in a position to show a time. This test requires a written effort by the patient but is completed in less time than the MMSE or SPMSQ. More practically, the course of delirium can be tracked by asking the patient to perform simple tests of attention such as the digit span (patient repeats 3–5 digits spoken by the interviewer at 1 s intervals in a monotone voice). Patients with delirium usually cannot complete the 5-digit span. The value of identifying patients at risk for delirium (e.g., dementia at baseline, sensory impairments, dehydration, or severe illness) is underscored by studies in hospitalized patients, which shows that delirium can be prevented. Effective steps in preventing delirium include improving hydration and calorie intake, improving hearing and vision with aids and appliances, providing cognitive stimulation such as reality orientation and therapeutic activities, and avoiding drugs with psychopharmacological properties such as benzodiazepines (12).

Although symptoms overlap, dementia and depression differ from delirium. Dementia is the development of multiple cognitive deficits that include memory impairment and at least one of the following cognitive disturbances: aphasia, apraxia, agnosia, or a disturbance in executive functioning. The cognitive deficits must be sufficiently severe to cause impairment in occupational or social functioning. Unlike delirious patients, those with dementia are usually alert and attentive and have a normal level of consciousness. Depressed patients are alert and attentive but often refuse to answer questions or to participate in ADL; they also have a dysphoric mood. Depressive symptoms are predictive of functional decline in elderly hospitalized patients and appear to be independent predictors of adverse effects on physical functioning following hospitalization. Although depression is not usually resolved during a short hospital stay, appropriate drug and supportive therapies can be initiated and continued after discharge. Depressive symptoms are detected with questions derived from screening instruments such as the Geriatric Depression

Scale (GDS, short-form) (19), which is a 15-item questionnaire where the presence of six or more depressive symptoms at admission is predictive of functional decline during hospitalization (20).

### *Sensory Deficits*

Vision impairment can reduce the patient's self-care ability, increase the patient's reliance on others for assistance, and increase caregiver burden. Vision and hearing deficits are also risk factors for incident delirium in hospitalized elderly patients. Visual impairment can be identified by asking any one of the following questions: "Do you have difficulty driving, watching television, reading, or doing any of your daily activities because of your eyesight?" Corrective lenses, large-print reading materials, and vision rehabilitation are helpful aids to vision. Hearing impairment can be detected through conversation with the patient. Significant hearing loss is present when a patient is unable to repeat three words whispered from 12 in. when the opposite ear is covered. Hearing can be augmented with aids and devices such as handheld amplifiers and headsets.

### *Nutritional Status*

Protein-calorie malnutrition is present in 20–40% of elderly hospitalized medically ill patients and is common with both acute and chronic infections (see also Chapter "Nutrition and Infection"). Protein-calorie malnutrition is associated with functional dependency and contributes to the excess risk of death from chronic diseases. The clinical features of malnutrition are often confounded by the effects of chronic disease that result in cachexia, anemia, and low serum albumin levels. However, objective anthropometric measurements such as scapular skin-fold thickness, body mass index, and biochemical measures of nutrition can help confirm the diagnosis of malnutrition. Malnutrition can be suspected on clinical grounds in patients who report a significant history of weight loss in the previous 6 months and who have physical findings suggestive of malnutrition (loss of subcutaneous fat, muscle wasting, ankle edema, sacral edema, and ascites). Body mass index ( $\text{weight (kg)/[height (m)]}^2$ ) below 19 is strongly predictive of mortality and is consistent with malnutrition. Undernutrition (suboptimal calories) during hospitalization is associated with functional decline, mortality, and delirium (12). Nutritional interventions, especially enteral supplementation with balanced liquid formulas, are associated with better functional outcomes. As older patients with infections often have anorexia or are unable to feed themselves independently, a concerted effort to assure adequate nutrition by enteral or parenteral routes is warranted to prevent further functional decline and

adverse outcomes of treatment. Patients at risk for aspiration pneumonia should be carefully assessed for oropharyngeal dysphagia. When patients are at risk for aspiration pneumonia, formal evaluation of swallowing, often complemented by a modified barium swallow, is useful. Patients with dysphagia for liquids may require a mechanical soft or pureed diet or thickened liquids in order to safely swallow and to reduce risk of aspiration.

### ***Social Supports***

Family members and close friends can be instrumental in helping to assure the patient's safe return to home from the hospital. Following treatment for an infection, patients who lack social support are more likely to require at least short-term transfer to a skilled nursing facility for rehabilitation. Patients with good supports and adequate health insurance might be able to receive home infusion therapy for continued antibiotic treatment (e.g., in treating endocarditis or osteomyelitis). The patient's primary caregiver is identified, and the social worker or case manager will help to identify the best post acute location for the patient. Home health care is a reasonable alternative when patients and their families prefer to receive restorative services at home. Patients who are functionally impaired and lack adequate social supports will likely require placement in a long-term care facility. Terminally ill patients can be admitted to palliative care (hospice) programs either in hospital or home.

### ***Special Settings***

Infections in postacute care (skilled nursing facilities, subacute units, long-term care nursing home) settings require special considerations. Functional assessment of these elderly residents before and after transitions in care is important for identifying residents who are vulnerable to functional decline during an infection, for evaluating the effect of the infection upon physical functioning, and for monitoring the impact of interventions to restore function following an infection. Functional assessment that includes more than the BADL and IADL is clinically necessary and mandated by state and federal regulation (Minimum Data Set). Regulatory requirements necessitate the assessment of cognitive and physical functioning upon admission to the facility and at prescribed periods, usually every 3 months. A significant change in function triggers a reassessment in order to develop a new plan of care. The assessment includes several other domains of functioning and health such as mood and behavior and the documentation of clinical events such as falls. Infections in the long-term care setting often impair the older person's ability to perform ADL and are one clinical indication for transferring a resident to the hospital.

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# Principles of Antimicrobial Therapy

Jay P. Rho

## Key Points

- Early and rapid diagnosis of infection and prompt initiation of appropriate antimicrobial therapy are fundamental to reducing the mortality and morbidity from infections.
- Guidelines exist that list minimum criteria for initiation of antimicrobial therapy, particularly in long-term care facilities.
- Recognition of certain age-related physiologic, pharmacokinetic, and pharmacodynamic changes can help optimize antimicrobial dosage regimens and minimize adverse effects.
- Prevention of antimicrobial resistance in healthcare settings requires an integrated strategy focusing on the following: preventing infection, diagnosing and treating infection effectively, using antimicrobials wisely, and preventing transmission.
- A majority of adverse drug events could be prevented by simply adjusting antimicrobial dosages for diminished renal function.

## Introduction

Until the direct observation that an airborne bacillus could inhibit the growth of another bacteria (antibiosis) by Louis Pasteur and Robert Koch in 1877, the therapy for infections remained empirically antidotal. Further research into the curative properties of moldy substances led to the discovery of penicillin in 1929 and to the development of the sulfonamides in the early 1930s, fully establishing the therapeutic nature of antibiotics. Prontosil, the first commercially available antibacterial agent,

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was discovered at the Bayer Laboratories in Germany and developed by the German physician Gerhard Domagk, who, in desperation, gave a dose of prontosil to treat his own daughter who was suffering from a deadly streptococcal infection (1). Following World War II, pharmaceutical companies in the United States began intensive research and development on molds and soil bacteria that could be synthesized into antibiotics. In the late 1940s through the early 1950s, three important new antibiotics were discovered: streptomycin, chloramphenicol, and tetracycline, marking the golden age of antimicrobial development.

Looking back over the past 60 years, a total of 10 new classes of antibiotics have been discovered, but only two of these have been discovered in the past 40 years. Since 1998, only 10 new antibiotics have been approved by the Food and Drug Administration (FDA), and of the 10 only two are considered novel. In 2002, the FDA approved 89 new drugs none of which was an antibiotic. The continued evolution of resistance to antibiotics has led to a growing consensus that new approaches to antimicrobial development such as genomics, is needed. However, the current perception by the pharmaceutical industry regarding this form of technology is that it is an extremely costly and a risky investment (2). Strictly from an economic perspective, it is estimated that an aggressive research and development program requires between 8 and 10 years and an investment of \$800 million to \$1.7 billion to bring forth any new drug to market. Because resistance to a new antibiotic can develop rapidly and shorten the commercial life span, antibiotics are generally considered a poor risk for return on investment. With fewer and fewer antibiotics making it through the FDA pipeline, it has become increasingly imperative that the judicious use of existing antibiotics be exercised to avoid further erosion of the antimicrobial armamentarium.

## **Approach to Antimicrobial Therapy**

Although the approach to antimicrobial therapy in the elderly population can differ from the approach utilized in the general or younger population, the guiding principles for the treatment of infection generally apply to both populations. These include the early and rapid diagnosis of infection, the prompt initiation of broad empirical coverage of suspected pathogens followed by the narrowing or discontinuation of antimicrobial coverage based on clinical status and definitive identification of the pathogen. The challenge associated with the initiation of prompt antimicrobial therapy in the elderly includes delays in early detection and diagnosis of infection. In elderly patients, many hallmark signs of infection may be absent or blunted. Elderly patients may not exhibit a febrile response or, when febrile, have a limited response compared with a younger patient. The early diagnosis of infection can be further hindered by difficulties observing cognitive impairment or by obtaining specific complaints from elderly patients that present with numerous comorbidities (3).

The appropriate selection of an antimicrobial agent is based on a number of criteria that includes the following: the proper identification of the pathogen, the site



of infection, the known antimicrobial resistance patterns, and the unique pharmacokinetics and pharmacodynamics characteristics of the agent as well as the potential risk of harm to the patient. The following questions should be considered before prescribing an antimicrobial agent:

- Is an antibiotic indicated?
- Have appropriate specimens been obtained, examined, and cultured?
- What pathogens are most likely?
  - Which antibiotic will provide the best choice based on pharmacokinetics, toxicology, cost, narrowness of spectrum?
- Is an antibiotic combination appropriate?
- What is the best route of administration?
- What is the appropriate dose?
- Will initial therapy require modification after culture data are returned?
- What is the optimal duration of treatment, and is development of resistance during prolonged therapy likely to occur?

A broad empirical antimicrobial regimen should be directed initially against the most likely pathogens and, at the suspected site of infection, sufficient dosages administered to achieve the desired therapeutic concentrations (4). Evidence suggests that the selection of antimicrobial therapy and the timing of its administration are important determinants of death for critically ill patients with serious infections. The choice of a specific empirical antimicrobial regimen should be based on the severity of the patient's illness, the nature of underlying diseases, prior exposures to antimicrobials, and the history of drug allergies. Most infections can be treated with a single antimicrobial agent. In a meta-analysis of 64 randomized trials of patients with sepsis, combination therapy that included an aminoglycoside and a beta-lactam antibiotic offered no significant benefit over single beta-lactam therapy on the basis of all-cause mortality and bacteriologic failure (5). The combination of two or more antimicrobial agents may be useful in certain clinical situations (1) to broaden the antimicrobial spectrum to cover all potential or known pathogens, (2) to delay or prevent the emergence of resistant microbial strains, (3) to enhance the antimicrobial effect of another drug against a specific organism (e.g., synergism), or (4) to reduce the dose of an agent to avoid toxicity. Broadening the antimicrobial spectrum to cover all potential or known pathogens is particularly important in treating mixed infections. Combination treatment with an extended-spectrum beta-lactam and a macrolide has been reported to improve outcome compared with that achieved with fluoroquinolone monotherapy in patients hospitalized with severe community-acquired pneumonia (6).

Minimum criteria for initiating systemic antibiotics for bacterial infections in long-term care facilities (LTCF) have been proposed by a consensus group of physicians, geriatricians, microbiologists, and epidemiologists (7). These guidelines emphasize the importance of initiating therapy only when there is a clear potential clinical benefit. Empirical regimens for common infections found in LTCF residents such as skin and soft-tissue infections, respiratory infections, and urinary infections as well as fever of unknown origin were outlined. Other potential

infections such as intravenous catheter-related infections or infections of mucous membranes and conjunctivae, topical antibiotic use, the use of antiviral and antifungal agents, prophylactic antibiotics, and the chronic suppressive antibiotics were not addressed (7).

## **Antimicrobial Resistance**

The increasing prevalence of antimicrobial-resistant pathogens has become a critical problem in both developed and underdeveloped nations. The emergence of *Staphylococcus aureus* with decreased sensitivity to vancomycin (8), worldwide presence of *Streptococcus pneumoniae* highly resistant to high-dose penicillin (9), and unabated progression of multiply-resistant *Myobacterium tuberculosis* (10) present unprecedented challenges for clinicians. It is estimated that over half of all nosocomial infections occurring in the United States are due to antibiotic-resistant organisms. Antimicrobial resistance develops when exposure to the agent fails to completely eradicate the infection. Resistance in bacteria can be intrinsic or acquired. Molecular mechanisms that contribute to resistance include enzymatic inactivation or modification, decreased uptake, altered target site, and bypass pathways. Multiple-drug resistance is generally due to conjugal transfer of plasmids containing multiple resistant genes. Genetic mutations may increase resistance by altering drug targets, destroying antimicrobials, and enhancing drug efflux (11). Evidence-based guidelines for the prevention of antimicrobial-resistant infections in healthcare settings have been published by the Centers for Disease Control and Prevention (CDC); however, clinician adherence to these guidelines is not optimal. The CDC has campaigned to improve practice behaviors by emphasizing four integrated strategies: preventing infection, diagnosing and treating infection effectively, using antimicrobials wisely, and preventing transmission (12). The importance of considering antibiotic resistance when treating at-risk populations such as the elderly is highlighted by their greater vulnerability to the adverse consequences of antibiotic resistance.

## **Antimicrobial Pharmacology**

The pharmacological activity of antimicrobial inhibition is often described as bacteriostatic or bactericidal. The term “bacteriostatic” describes a drug that temporarily inhibits the growth of a microorganism. The therapeutic success of an antimicrobial agent often depends upon the participation of host defense mechanisms. When the drug is removed, the organism will resume growth and infection or disease may recur. The term “bactericidal” is applied to drugs that cause the death of the microorganism; however, the terms are relative, not absolute. Sometimes prolonged treatment with bacteriostatic drugs can kill certain microbial populations.

In a host with adequate defenses, a bacteriostatic effect may be sufficient to result in eradication of the infection.

Although there are reports that both the pharmacokinetics and pharmacodynamics of antimicrobial agents are affected by age, the basic principles of therapy are no different from those applicable in younger patients (13). Consideration of the pharmacokinetic changes observed in the elderly patient (Table 1) can help guide decisions about the dosing and the monitoring of antimicrobial agents detailed in subsequent chapters.

### *Absorption*

Peak serum concentration of an antibiotic is achieved most rapidly when administered through the intravenous route. Other routes such as intramuscular and oral are less rapid and less reliable. The rate and extent of oral drug absorption can differ between individuals due to variability in gastric motility, gastric emptying time, and stomach acidity, which influence dissolution and absorption of drugs. Changes in intestinal blood flow, a primary route of drug removal from the gut into the circulation, can also influence oral drug absorption.

There are several age-associated physiologic changes that may affect the absorption of drugs. Decrease in acid production and increase in gastric pH that can modify the ionization and solubility of some drugs can result from alterations in parietal and gastric cells in older individuals. Other factors that may alter the absorption of drugs from gastrointestinal tract are the blood flow of splanchnic vessels and quantity of mucosal cells involved in absorption of drugs, which both decrease with age. Atrophy of gastric mucosa and decreased gastrointestinal motility in the elderly

**Table 1** Physiological changes associated with aging

Pharmacokinetic parameter	Physiological change with aging
Absorption	<ul style="list-style-type: none"> <li>↑ Gastric emptying</li> <li>↓ Gastric acidity</li> <li>↓ Gastrointestinal motility</li> <li>↓ Absorptive surface</li> </ul>
Distribution	<ul style="list-style-type: none"> <li>↓ Lean body mass</li> <li>↑ Body fat</li> <li>↓ Serum albumin</li> <li>↑ α1-acid glycoprotein</li> </ul>
Elimination	<ul style="list-style-type: none"> <li>↑↓ Enzyme activity</li> <li>↓ Hepatic (liver) blood flow</li> <li>↓ Renal (kidney) blood flow</li> <li>↓ Glomerular filtration rate</li> <li>↓ Tubular secretion</li> </ul>

↓ decrease activity or function, ↑ increase activity or function, ↑↓ may increase or decrease activity or function

may not have an impact on drug absorption, since this process is a simple passive diffusion (in most cases) that depends on concentration gradient or lipid-water partition coefficient. Antimicrobials such as itraconazole, sulfonamides, dapsone, and pyrimethamine exhibit reduced absorption in this setting (14).

## *Distribution*

Most sites of infection are extravascular and treatment of infections requires the distribution of the antimicrobial agent out of the bloodstream and into interstitial and sometimes intracellular fluid. Several factors that may affect the distribution of drugs include body composition, plasma protein concentration, and distribution of blood flow to various organs and tissues. The ability of a drug to distribute to extravascular space depends on its lipid solubility. Lipid-soluble drugs such as chloramphenicol, metronidazole, and rifampin penetrate these areas to a greater extent than water-soluble drugs such as beta-lactams, aminoglycosides, and vancomycin (15).

Reduced total body weight and notable age-associated change in body composition result in alteration of drug distribution in older individuals. In addition to decline in total body water with age, continuous loss of lean body mass with aging also contributes to significant change in body composition. Age-related decrease in muscle and lean body mass is compensated by increase in total fat. The proportion of adipose tissue relative to total body weight is estimated to increase 18–33% in elderly men and 33–48% in elderly women (16). Due to this increase in percentage of body fat, higher serum concentration of hydrophilic drugs are distributed primarily to lean body mass or body water. Conversely, the apparent volume of distribution of lipid-soluble drugs in turn increases with age. If the dose is unchanged in this population, then increased volume of distribution can result in drug accumulation and prolonged effect. Other factors suggested to alter the drug distribution in the geriatric patient include reduced physical activity and variation in tissue permeability.

The decline in total body water, which occurs 10–15% over the adult life span, leads to a smaller volume of distribution for water-soluble drugs. Volume of distribution of a drug represents an extent of drug distribution to tissues relative to the plasma volume and also the relationship between plasma drug concentration and the total amount of drug in the body. For drugs that distribute extensively into total body water (i.e., hydrophilic drugs), reduced volume of distribution has been reported in the elderly (17). Without dosage adjustment of these drugs in the elderly patient, the reduced volume of distribution can lead to higher drug concentration per unit volume of drugs and subsequent drug toxicity. Due to the increase in volume of distribution in aging populations, the alterations in the area under the plasma concentration time curve (AUC) and plasma half-life is expected to influence the time above minimum inhibitory concentrations (MIC) for antimicrobial agents.

The decrease in plasma albumin is also well known to alter both the volume of distribution and the free fraction of highly protein-bound drugs in the elderly.

Due to lower dietary intake of protein and reduced synthesis in the liver, the reduction in serum albumin levels are reported to be up to 25% in older population. In the presence of lower serum albumin concentration, drug interactions affecting the displacement of drugs from albumin have been reported to increase in the elderly due to multiple-drug therapy (18).

### *Elimination*

Most antimicrobial agents, including most beta-lactams, aminoglycosides, tetracyclines, vancomycin, and sulfonamides, are excreted by the kidneys. The two most important physiologic processes involved in renal excretion are the glomerular filtration and active tubular secretion at the level of proximal tubules. Renal reabsorption, a passive process by which drugs enter back into the body through the peritubular capillary network, also determines the renal clearance of drugs.

Parameters of renal function such as glomerular filtration rate (GFR), renal blood flow, and creatinine clearance decreases by 50% by 90 years of age (19). This reduction is due to changes in several structural and functional aspects of the kidney in the elderly. Age-associated decline in kidney volume and weight correlates well with the loss of total number of glomeruli. Decrease in renal blood flow due to age-related intrarenal vascular changes and loss of tubular excretory and reabsorptive capacity in aging population occur simultaneously with the decline in GFR. Aside from the usual decline of renal function with age, the geriatric patients are at risk for further decline in renal function because of pathologic processes commonly seen in this population (e.g., dehydration, congestive heart failure, diabetes mellitus, and hypertension).

### *Pharmacodynamics*

Pharmacodynamics, as it applies to antimicrobial agents, describes the pharmacologic effects of the drugs on receptors, tissues, and organ systems beyond strict drug concentrations. Antibiotics display two types of antibacterial activity: time-dependent killing and concentration-dependent killing. The time-dependent group of antibacterials includes the beta-lactams as well as cephalosporins, macrolides and clindamycin. Bacterial killing for these agents correlates poorly with peak serum concentration; rather, the best predictor of clinical success is the amount of time the antibacterial drug concentration remains above the minimum inhibitory concentration (MIC). The concentration-dependent killing group of antibacterials include the aminoglycosides and fluoroquinolones. The rate and extent of bactericidal activity of these drugs increases proportionally as drug concentrations increase, even when the concentrations are substantially above the MIC of the organism. The ability of an antibiotic to exert persistent suppression of bacterial growth even when antibiotic

concentration fall below the minimal inhibitory concentration is described as a postantibiotic effect (PAE). PAE effects observed with aminoglycosides administered as a larger single-daily dose allows for extended dosing intervals with efficacy similar to more frequent shorter dosing intervals (15, 20).

### ***Drug Interactions***

Drug interactions constitute an often predictable and avoidable cause of adverse drug events (21). Polypharmacy is prevalent in the elderly population with 23% of non-institutionalized women and 19% of non-institutional men age 65 years of age and older using more than five prescription medications, many of which have narrow therapeutics indices (22). The mechanisms of adverse drug interactions are varied, but the inhibition or induction of drug metabolism is considered of highest importance. Oxidative metabolism by cytochrome p450 enzymes is a primary method of drug metabolism. Inhibitors and inducers of the hepatic monooxygenase system include the following antimicrobial agents: fluconazole, miconazole, ketoconazole, erythromycin, clarithromycin, sulphonamides, and fluorquinolones. Numerous cases of antimicrobials interacting with cardiac medications such as digoxin, verapamil, and diltiazem have been reported. Digoxin concentrations may be increased by concomitant administration of erythromycin, clarithromycin, and tetracyclines. When warfarin is combined with metronidazole, co-trimoxazole or voriconazole, the international normalized ratio (INR) may be increased several-fold, leading to a higher risk of bleeding. Use of rifampin and nafcillin have been shown to enhance warfarin metabolism and reduce the INR placing a patient at greater risk of a thromboembolism (23).

### ***Adverse Drug Events***

Antimicrobial agents are among the most frequently prescribed drugs today, second only as a class to cardiovascular drugs. Adverse effects can range from fever and nausea to major allergic reactions including anaphylaxis. Antibiotic-associated colitis is a common side effect with the use of antibiotics known to disrupt the normal balance of the intestinal flora such as clindamycin and beta-lactam antibiotics. Older age is a risk factor for *Clostridium difficile* associated disease (CDAD), as the incidence increases in those older than 60 years of age. It is well documented that elderly patients experience more frequent adverse drug reaction (ADR) than their younger counterparts. Polypharmacy, comorbidities, and difficulty with medication adherence can combine to significantly increase ADE risk. Insufficient dosage adjustments for an elderly patient's renal function remain a significant contributor to antimicrobial ADEs. A study of antibiotic dosage errors involving 1,044 hospitalized patients >80 years of age revealed an overall dosing error of 34% (24).

## Antimicrobial Agents

### *Beta-Lactams*

Beta-lactams (penicillins, cephalosporins, carbapenems) are bactericidal agents that share a common four-membered beta-lactam ring, which may be fused to five- or six-membered heterocyclic rings. Beta-lactam agents exert their antibacterial action by binding to specific enzymatic proteins within the bacterial cell membrane called penicillin binding proteins (PBP). PBPs are responsible for the normal synthesis and organization of the bacterial cell wall. Attachment of beta-lactams to specific PBPs can block transpeptidation of peptidoglycan a critical step in cell wall synthesis. Furthermore, attachment to specific PBPs can result in the activation of autolytic enzymes in the cell wall, which result in lesions that cause bacterial death. Beta-lactams can be classified according to their spectrum of antibacterial activity and pharmacokinetic properties. Select beta-lactam antibiotics (penicillins, cephalosporins, carbapenems, monobactams, and beta-lactamase inhibitors) may be useful in the management of infections in elderly patients because of their broad spectrum, their favorable pharmacokinetics, and their favorable safety profiles. These would include parenteral cefotetan, ceftriaxone, cefoperazone, and cefipime as well as oral agents such as penicillin, dicloxacillin, amoxicillin, amoxicillin-clavulanate, cephalexin, cefuroxime axetil, and cefixime (25).

### *Macrolides*

The macrolides are a group of antibacterial agents that share a common macrolide ring, a large macrocyclic lactone ring to which one or more deoxy sugars may be attached. Macrolides exert their antibacterial effects by inhibition of bacterial protein synthesis by binding reversibly to the 50S subunit of the bacterial ribosome, thereby inhibiting translocation of peptidyl tRNA (26). The macrolides have traditionally been considered concentration-independent agents. Erythromycin, clarithromycin, and azithromycin have a limited role in the management of infections in the elderly in general. Clarithromycin and azithromycin have more favorable dosing regimens, improved antimicrobial activity, and lower gastrointestinal intolerance compared with erythromycin. These agents are moderately active against most strains of streptococci, methicillin-sensitive *S. aureus*, anaerobes, *Moraxella catarrhalis*, *Haemophilus influenzae*, *Legionella*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae* as well as atypical mycobacteria such as *Mycobacterium avium* complex. The primary means of bacterial resistance to macrolides occurs by post-transcriptional methylation of the 23S bacterial ribosome RNA. This acquired resistance can be either plasmid-mediated or chromosomal.

Limited data are available regarding pharmacokinetics of these newer macrolides in elderly persons; decrease in drug clearance has been attributed to reduce renal

clearance. The indications for the newer macrolides in elderly persons are no different than for the general population (20).

### ***Ketolides***

Telithromycin is the first FDA-approved member of a new class of antimicrobials called the ketolides. Telithromycin is similar in chemical structure to the macrolides including the same basic 14-member lactone structure as erythromycin. Telithromycin differs in chemical structure from macrolides in the replacement of the cladinose ring with a ketone group at position 3 and the addition of an 11–12 cyclic carbamate. These chemical modifications enhance telithromycin's spectrum of activity while maintaining the acid stability of the newer macrolides (27).

Telithromycin is active against common community-acquired respiratory pathogens including penicillin- or macrolide-resistant strains of *S. pneumoniae*. Telithromycin is also active against the atypical, intracellular pathogens *M. pneumoniae*, and *Legionella pneumophila*. Telithromycin has poor activity against other gram-negative bacilli, including Enterobacteriaceae and *Pseudomonas aeruginosa* (28).

Since 2006 following several reports of patient deaths and liver failure, major safety concerns have arisen. Other major safety concerns include the potential for QTc interval prolongation on electrocardiogram, and the potential for exacerbation, including increased risk for ventricular arrhythmias and torsades de pointes. There have been reports of fatal and life-threatening respiratory failure in patients with myasthenia gravis associated with the use of telithromycin. The FDA has required a "black box warning" be placed in the package insert advising physicians and patients this drug is contraindicated in patients with myasthenia gravis (29).

### ***Fluoroquinolones***

Since the mid-1980s, fluoroquinolone (also called quinolones) antibiotics have been available. Their popularity has continued to grow over the last 20 years based on their broad spectrum of antimicrobial activity, good absorption from the gastrointestinal tract, unique mechanism of action (inhibition of DNA gyrase), favorable pharmacokinetic properties, and a good safety profile (30).

As a group, the fluoroquinolones have excellent in vitro activity against a wide range of gram-positive bacteria and many gram-negative bacteria such as, Enterobacteriaceae and *Aeromonas*, *Brucella*, *Camphylobacter*, *Haemophilus*, *Legionella*, *Moraxella*, *Neisseria*, and *Vibrio*. These agents are active against *P. aeruginosa* but are significantly less active against other pseudomonal species, including *P. capacia* and *P. fluorescens*. Ciprofloxacin is the most active quinolone against *P. aeruginosa*. The newer generation fluoroquinolones have activity against gram-positive bacteria, including *S. pneumoniae* and staphylococcal species



(i.e., methicillin-sensitive *S. aureus* and coagulase-negative species). The fluoroquinolones have less activity against streptococcal species and enterococci.

In general, these agents have very poor activity against anaerobes and *Nocardia* organisms. In the treatment of community-acquired pneumonia, there has been an increasing use of these agents (31). Ciprofloxacin and ofloxacin are active against many species of *Mycobacterium*, including *M. tuberculosis*, *M. kansasii*, *M. fortuitum*, and *M. xenopi*. Ciprofloxacin was initially introduced to North America in 1987. Fluoroquinolones are used because they allow the convenience of oral therapy with an agent with good bioavailability, they are easily administered by one- or twice-daily dosing, they are perceived to be safe, and they have a wide spectrum of activity. In the elderly, fluoroquinolones are useful in the treatment of complicated urinary tract infections, bacterial prostatitis, skin and soft tissue infections, pneumonia, malignant external otitis, and bacterial diarrhea caused by susceptible pathogens. The newer generation fluoroquinolones (e.g., levofloxacin, gatifloxacin, moxifloxacin) with improved gram-positive (including *S. pneumoniae*) activity over that of the older agents in this class are now considered agents of choice for the treatment of community-acquired pneumonia in adults, including the elderly.

Fluoroquinolones are considered to be concentration-dependent in their antibacterial killing activity. Fluoroquinolones have been shown to display prolonged PAE effects against gram-negative bacilli in the range of 1.5–2.5 h. Adverse effects of quinolones in the elderly occur in 5–15% of cases, including gastrointestinal (nausea, vomiting, and diarrhea) and central nervous system effects such as dizziness, headache, and insomnia. With the frequent quinolone use, resistance of organisms has increased. Resistance via mutations in the genes encoding topoisomerase II and IV along with increased drug efflux is common in clinical isolates. Quinolone resistance (methicillin-resistant *S. aureus* (MRSA), *Enterococcus faecalis*, *S. pneumoniae*, and *P. aeruginosa*) complicates management of infections by requiring parenteral therapy with other antibiotics for organisms resistant to these oral agents as well as increasing the burden of resistant organisms.

### ***Co-trimoxazole***

Co-trimoxazole is an antibiotic combination of trimethoprim and sulfamethoxazole, in the ratio of 1 to 5, commonly prescribed in the elderly for urinary tract infections, chronic bacterial prostatitis, lower respiratory tract infections, and bacterial diarrhea caused by susceptible pathogens. Co-trimoxazole exerts its antibacterial effects by inhibiting successive steps in the folate synthesis pathway. Sulfamethoxazole acts as a false-substrate inhibitor of dihydropteroate synthetase. Trimethoprim acts by interfering with the action of bacterial dihydrofolate reductase and inhibiting synthesis of tetrahydrofolic acid. Data are limited on the pharmacokinetics of this drug in elderly persons (32). Oral drug absorption does not appear to be affected by age. In older persons, renal clearance of trimethoprim is decreased. The recommended doses for use in the elderly are comparable to those prescribed in younger

persons; with renal impairment and a creatinine clearance of less than 30 mL/min but greater than 15 mL/min, the dosage is reduced by half. The drug should be avoided if the creatinine clearance is less than 15 mL/min.

### ***Aminoglycosides***

The aminoglycosides are a group of bactericidal agents originally obtained from various *Streptomyces* spp. that include gentamicin, tobramycin, streptomycin, and amikacin among others. These agents bind irreversibly to certain receptors on the 30S subunit of bacterial ribosomes and cause several changes in protein synthesis by (1) interfering with the “initiation complex” of peptide formation; (2) inducing the misreading of the code on the mRNA template, which causes incorporation of incorrect amino acids into the peptide, and (3) causes the breakup of polyomes into nonfunctional monosomes. Aminoglycosides exhibit rapid, concentration-dependent killing and are rapidly bactericidal against staphylococci and gram-negative aerobic bacteria, including *Pseudomonas* spp. Aminoglycosides can also be used as adjunctive therapy with other agents (e.g., beta-lactams) for treatment of serious or life-threatening infections such as *S. aureus* and enterococcal endocarditis. Aminoglycosides must be prescribed with caution in the elderly because of the well-documented risks of ototoxicity (generally irreversible) and nephrotoxicity (generally reversible) associated with these agents and the availability of safer and less toxic drugs with comparable spectra (i.e., cephalosporins, monobactams, carbapenems, beta-lactam/beta-lactamase inhibitor combination antibiotics, and quinolones). Should an aminoglycoside be prescribed, careful calculation of the dose should be conducted based on the patient’s creatinine clearance. Nephrotoxicity is less likely with once-daily dosing compared with the conventional every 8-h dosing and is usually reversible. Nephrotoxicity, however, may lead to high serum levels of aminoglycosides, which can cause irreversible ototoxicity. Risk of ototoxicity increases with age and is highest in patients with pre-existing hearing deficiencies. Thus, aminoglycoside use in elderly patients should be reserved for those with serious or life-threatening infections that require hospitalization and are caused by pathogens susceptible to aminoglycosides (33).

### ***Miscellaneous Antibiotics***

Other antimicrobial agents, deserving brief mention, that could be prescribed for the elderly patient include vancomycin, quinupristin + dalfopristin (Synercid®), linezolid (Zyvox®), daptomycin (Cubicin®) and metronidazole. Vancomycin is a glycopeptide antibiotic used primarily for gram-positive bacterial infections. It is highly active against staphylococci (including MRSA) and streptococci (including vancomycin-sensitive enterococci). In the elderly, studies have indicated that reduced

clearance of vancomycin is a consequence of reduced systemic and renal clearance as well as enhanced tissue binding of the drug. Lower parenteral doses are recommended for the frail elderly, and the dose should be adjusted according to the serum peak and trough levels as well as the creatinine clearance (34). The side effect profile in the elderly is no different from that in the general population.

Quinupristin–dalfopristin, a streptogramin, is indicated in adults, including the elderly for the treatment of serious and life-threatening or bacteremic infection with vancomycin-resistant enterococci (VRE) and complicated skin and skin structure infection with methicillin-susceptible *S. aureus* and *Streptococcus pyogenes*. The pharmacokinetics of this agent is similar to that in younger adults (35).

Linezolid, an oxazolidinone, is active against infections caused by sensitive gram-positive bacteria as well as MRSA and VRE. This agent's availability, both in parenteral and oral formulations, as well as its relatively safe profile, is particularly advantageous in management of infections caused by such gram-positive-resistant organisms commonly encountered in elderly patients (36).

Daptomycin is a cyclic lipopeptide indicated for the treatment of complicated skin and skin structure infections caused by susceptible gram-positive organisms such as *Staphylococcus* (including MRSA) and *Streptococcus*. Daptomycin should not be used in the treatment of pneumonia. Because daptomycin is eliminated primarily by renal excretion, patients with creatinine clearance less than 30 mL/min should receive a reduced dosage. In geriatric patients with normal renal function, no dosage adjustment is necessary.

### ***Antituberculous Agents***

Currently approved antituberculous drugs in the United States include the following: isoniazid, rifampin, pyrazinamide, ethambutol, ethionamide, streptomycin, amikacin, kanamycin, capreomycin, and paraamino salicylic acid. Fluoroquinolones are not currently labeled for use in tuberculosis but are used relatively commonly to treat drug-resistant tuberculosis. First-line agents in the elderly include isoniazid, rifampin, ethambutol, and pyrazinamide. Under specific situations, rifabutin and rifapentine may also be considered first-line agents. When the appropriate indications are present, isoniazid should also be used for the treatment of latent tuberculosis infection (37).

### ***Antifungal***

Similar to younger adults, the commonly prescribed systemic antifungal agents in the elderly include the following: amphotericin B, fluconazole, itraconazole, and voriconazole. Amphotericin B and liposomal/lipid formulations of amphotericin B are the standard of treatment for systemic fungal infections. Because of potential

toxicity of amphotericin B to renal function in the elderly, this agent must be used with caution. Fluconazole, because of its relative safety and efficacy and excellent bioavailability when administered by parenteral and oral routes, is prescribed more often in aging individuals. Itraconazole and voriconazole, available by parenteral and oral formulations, are acceptable alternatives, when indicated (38).

### ***Antiviral Agents***

Three antiviral agents are available for the treatment of herpes zoster: acyclovir, valacyclovir, and famciclovir. All three are considered equally efficacious but valacyclovir and famciclovir are preferred over acyclovir because of enhanced oral bioavailability. Acyclovir, valacyclovir, and famciclovir are effective agents for the treatment of herpes simplex and herpes zoster infection. By administering these agents within the first 72 h of the onset of illness, pain from herpes zoster and chronic pain (postherpetic neuralgia) may be relatively diminished.

Four antiviral agents are available for the treatment of influenza A infections: amantadine, rimantadine, oseltamivir, and zanamivir. Each agent is considered equally efficacious. Within 48 h of illness onset, amantadine and rimantadine are recommended for influenza A infection in the ambulatory elderly to reduce the duration and severity of illness; in institutionalized elderly, these drugs are recommended for prophylaxis during an influenza A outbreak within the institution. Both drugs are continued for a minimum of 2 weeks or until approximately 1 week after the end of the outbreak. The neuraminidase inhibitors, zanamivir (Relenza<sup>®</sup>) and oseltamivir (Tamiflu<sup>®</sup>), are available for use in influenza A and B infections; efficacy and safety in elderly patients have not been extensively studied. In adults who have been symptomatic for no longer than 2 days, these drugs are used for the symptomatic treatment of uncomplicated acute illness caused by influenza A and B virus. Dosage adjustments based solely on age are not necessary for geriatric patients who are age 65 years and older. For the prophylaxis of influenza A or B virus infection in adults, Oseltamivir may be used as an adjunct agent along with the annual influenza virus vaccine. The safety and efficacy of zanamivir for the prophylaxis of influenza virus infection remains to be established (39).

### **Summary**

Despite the unique challenges facing clinicians who are prescribing antimicrobial agents in elderly patients, the fundamental principles of antimicrobial therapy still apply. Morbidity and mortality can be greatly reduced with the early initiation of appropriate empirical therapy followed by the appropriate narrowing of antimicrobial coverage after the determination of pathogen susceptibilities.

Knowledge of age-related changes in pharmacokinetic and pharmacodynamic parameters will help clinicians optimize antimicrobial dosing and minimize adverse drug events.

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# **Part II**

## **Common Infections**



# Sepsis

Timothy D. Girard

## Key Points

- Sepsis is an often deadly systemic inflammatory response to infection that occurs frequently among older patients due to multiple risk factors, including immunosenescence, comorbid illness, institutionalization, and instrumentation.
- Nonspecific or atypical symptoms are common among older patients with sepsis, and clinicians must have a high index of suspicion for sepsis when patients present with such symptoms.
- The diagnostic approach to an older patient with suspected sepsis primarily includes a systematic search for a microbiologic diagnosis.
- Though older patients are more likely to die from sepsis than younger patients, older patients often respond to aggressive therapy, including antibiotics, hemodynamic support, recombinant human activated protein C, and supportive measures.
- The Surviving Sepsis Campaign recently updated their evidence-based guidelines for the management of severe sepsis, and these guidelines should be applied to the care of older patients with sepsis.

## Epidemiology and Clinical Relevance

### *Incidence*

Sepsis, a syndrome of systemic inflammation that occurs in response to infection, is an often deadly manifestation of infection that is more likely to occur as a person ages.

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**Table 1** Definition and progression of sepsis<sup>a</sup>

Disorder	Definition
SIRS	The systemic inflammatory response to a variety of clinical insults, exhibited by at least two of the following: (1) temperature >38°C or <36°C, (2) heart rate >90 beats/min, (3) respiratory rate >20 breaths/min or PaCO <sub>2</sub> <32 mmHg, and (4) WBC >12,000 or <4,000/mm <sup>3</sup> or >10% immature (band) forms
Sepsis	SIRS and documented or suspected infection
Severe sepsis	Sepsis complicated by organ dysfunction
Septic shock	Sepsis complicated by hypotension (i.e., SBP <90 mmHg or MAP <60 mmHg) despite adequate fluid resuscitation

*Abbreviations:* SIRS systemic inflammatory response syndrome; WBC white blood cells; SBP systolic blood pressure; MAP mean arterial pressure

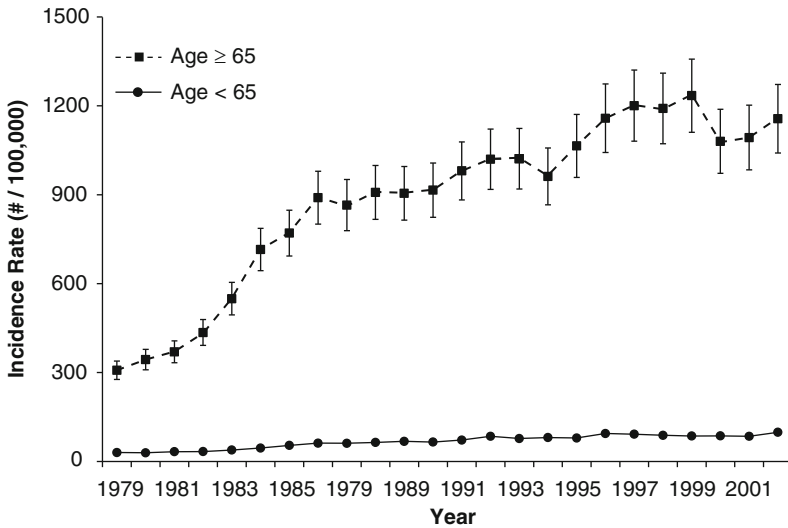
<sup>a</sup>American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference definitions (1)

Defined as a systemic inflammation response syndrome (SIRS) in the setting of infection, sepsis can progress rapidly and result in shock, multisystem organ failure, and death (Table 1) (1).

Nearly a decade ago, Angus and colleagues (2) reported that approximately 750,000 patients develop severe sepsis each year in the United States alone; it is likely that these figures now greatly underestimate the incidence of sepsis, which has continued to rise throughout the past decade (3, 4). Whereas the annual incidence of severe sepsis among all ages in 1995 was estimated to be 3.0 cases/1,000 population, older persons were dramatically more likely to develop sepsis; Angus et al. (2) estimated that 26.2 cases/1,000 population occurred among those >85 years. Martin and colleagues (5) subsequently confirmed these findings using data from the National Hospital Discharge Survey. Not only were patients ≥ 65 years of age 13 times more likely to have sepsis than younger patients, but this difference in risk has also increased over time. On average, from 1979 to 2002, the incidence of sepsis increased 9.5% per year among patients younger than 65 years of age but among those 65 years of age and older (Fig. 1) it increased 11.5% per year. In many other studies, the association between increasing age and sepsis has been well-documented (6, 7).

## **Prognosis**

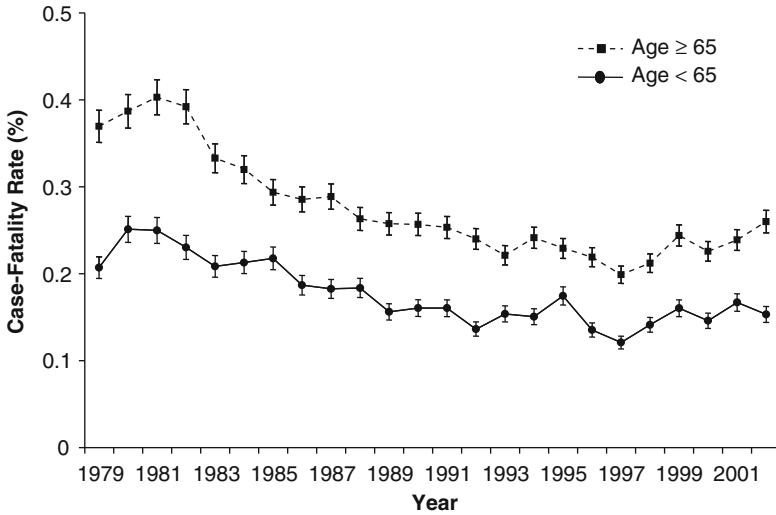
Sepsis is one of the 10 leading reported causes of death in the United States, and death certificates fail to capture a significant portion of sepsis-related deaths. In fact, Angus et al. (2) estimated that 9.3% of all deaths in the United States in 1995 were due to sepsis, such that sepsis killed as many people as acute myocardial infarction in that year. Death in patients with sepsis is usually a result of multiple organ dysfunction and shock (8); 25–30% of patients with severe sepsis will not survive (9), and 35–40% of those with septic shock will succumb to their illness (10).



**Fig. 1** Age-adjusted incidence rates of sepsis among hospitalized patients, stratified by age  $\geq 65$  (dashed line) or  $< 65$  (solid line). Points are mean values; I-bars represent the SEM. Figure from Martin et al. (5) with permission

Not only are older persons more likely to develop sepsis, but they are also at increased risk of death due to sepsis. In their large epidemiologic study, Angus et al. (2) found that 61.6% of patients  $\geq 85$  years of age survived severe sepsis compared with 90% of septic children who survived. Similarly, Martin et al. (5) determined that from 1979 to 2002, septic patients 65 years of age and older were 1.56 times more likely to die than younger septic patients but that case fatality rates are declining more rapidly over time among older patients than younger patients (Fig. 2).

Despite these findings, and those of several other studies of patients with sepsis and/or bacteremia showing older age is associated with an increased risk of death (6, 11, 12), the results of other investigations have cast doubt on the association between increasing age and mortality due to sepsis. For example, a smaller study of 406 patients with sepsis indicated that patients who died from sepsis were older than survivors, but older age was not an independent predictor of death after other factors were considered such as severity of illness, source of infection, and adequacy of empirical antibiotics (13). These findings can be reconciled with those of Angus et al. and Martin et al. by examining the findings of Knaus and colleagues (14). In a study of 1,195 patients with sepsis, age was independently associated with an increase risk of death, but the most important determinant of mortality was severity of illness (Table 2). Thus, smaller studies may be unlikely to note an association between increasing age and sepsis-related mortality though this association has been demonstrated in many large investigations.



**Fig. 2** Fatality rates of sepsis among hospitalized patients longitudinally from 1979 to 2002, stratified by age  $\geq 65$  years (dashed line) or  $< 65$  (solid line). Figure from Martin et al. (5) with permission

**Table 2** Association of acute physiology score and age with 28-day mortality in patients with sepsis

	N	28-Day mortality (%)	ARLL	CI
<i>Acute physiology score<sup>a</sup></i>				
0–40	152	12	1	1
41–60	330	22	1.99	1.14–3.45
61–80	348	36	4.27	2.48–7.37
81–100	218	45	5.88	3.31–10.43
101–120	75	64	15.67	7.90–31.08
120+	72	85	42.93	21.25–86.71
<i>Age (years)</i>				
0–44	184	26	1	1
45–54	116	34	1.33	0.75–2.36
55–64	203	33	1.59	0.97–2.62
65–74	315	35	1.61	1.01–2.55
75–84	285	41	2.31	1.45–3.70
85+	100	42	2.29	1.27–4.11

*Abbreviations:* N number; ARLL adjusted ratio of life length (multivariate results: larger ARLLs associated with shorter expected survival time; similar to odds ratio); CI confidence interval of ARLL; APACHE acute physiology and chronic health evaluation

Adapted from Knaus et al. (14) with permission

<sup>a</sup>Acute physiology score of APACHE III

## Clinical Manifestations

### *Pathogenesis and Pathophysiology*

Sepsis, a complex interaction of both inflammatory and anti-inflammatory responses, occurs when a toxic microbial stimulus (e.g., lipopolysaccharide, peptidoglycan, and other pattern recognition molecules) triggers the release of proinflammatory mediators. Tumor necrosis factor-alpha (TNF- $\alpha$ ), interleukin-1 (IL-1), and other cytokines and chemokines activate leukocytes, promote leukocyte-vascular endothelium adhesion, and induce endothelial damage (15). Subsequently, tissue factor is expressed from damaged endothelium and activated immune cells (especially macrophages), activating the tissue factor-dependent coagulation cascade, ultimately leading to the formation of thrombin and microaggregates of fibrin, platelets, neutrophils, and red blood cells, which impair capillary blood flow, decreasing oxygen and nutrient delivery (16).

Immunosenescence – changes in the immune system that occur with age – contributes to the increased susceptibility of older persons to infection (17). Although basic components of the innate immune system are well-maintained with aging, adaptive immunity is significantly impaired with increasing age such that cell-mediated immune responses are diminished. T cells in the elderly have limited proliferative capacity and impaired signal transduction after engagement with antigen presenting cells (18), and the relative absence of helper T cell function (due to impaired expression of co-stimulatory molecules important to B cell-T cell interactions) results in blunted antibody responses to infection (19).

Due to immunosenescence, numerous clinical factors that are common in older populations serve to compound the increased risk for infection. Older persons are more likely than their younger counterparts to have comorbid illnesses, conditions which often lead to instrumentation, hospitalization, or institutionalization in a long-term healthcare facility. Martin et al. (5) found that septic patients 65 years and older were twice as likely to have at least one comorbid medical condition than younger sepsis patients, and septic patients  $\geq 75$  years of age who were enrolled in the Protein C Worldwide Evaluation of Severe Sepsis (PROWESS) trial more often had coronary artery disease, chronic obstructive pulmonary disease, malignancy, and a history of recent surgery compared with younger septic patients (20). Urinary catheters, central venous catheters, tracheostomies, and other medical devices as well as the procedures required to place or remove them are common among older patients with comorbidities; each device and procedure creates a portal of entry for infection. In one study, for example, indwelling urinary catheters were the leading risk factor for bacteremia among 533 chronically institutionalized older patients (21). Even for older patients without exposure to medical devices, frequent visits to or residence in a healthcare facility represent a significant risk for infection. In both hospitals and in long-term care facilities, older patients are at high risk to become colonized or infected with antibiotic-resistant organisms (22). Whereas age alone is not necessarily an independent risk factor, older patients are more likely to have

risk factors for infection with resistant organisms; in a study of *Staphylococcus aureus* bacteremia, Rezende et al. (23) found that older patients were more often infected with methicillin-resistant *S. aureus* (MRSA) because these patients frequently had risk factors such as nursing home residence, recent hospitalization, recent antimicrobial, and indwelling urinary catheters (see also the chapter “Staphylococcal and Enterococcal Infections”).

Not only does advanced age increase the risk of infection and impair the immune response to it, but also increasing age predisposes older persons with infection to the inflammation and deranged coagulation that characterized sepsis. TNF- $\alpha$ , IL-6, and other proinflammatory cytokines reach higher concentrations in older septic patients than in younger patients with sepsis (24, 25). Similarly, D-dimer, activated factor VII, and other coagulation factors are elevated in older persons without any acute illness, indicating ongoing activation of inflammatory and coagulation pathways (26, 27). These findings may explain why older patients are more likely to develop sepsis when infected than younger patients; in one study of 832 patients with bacteremia, age  $\geq 50$  years was an independent risk factor for severe sepsis (6). In another study of 890 patients with community-acquired bacteremia, septic shock occurred in 39.1% of patients  $\geq 85$  years of age as compared with 26.1% of patients 65–84 years of age and 23.1% of patients  $<65$  years of age (28).

### *Symptoms and Signs*

Nonspecific or atypical clinical manifestations of infection occur frequently in older persons such that septic patients of advanced age may not present in the same manner as younger patients with sepsis. In fact, in a study of 105 patients with systemic infection, older patients (mean age, 80.4 years) had fewer symptoms overall than younger patients (mean age, 45.7 years) (29). Nonspecific symptoms may include altered mental status (e.g., delirium or coma), urinary incontinence, falls, anorexia, malaise, and generalized weakness. In a study of 811 patients with gram-negative severe sepsis, Iberti and colleagues (30) found that patients  $>75$  years of age had tachypnea and altered mental status more frequently than younger patients. Tachycardia and hypoxemia, on the other hand, were less common among older patients. A recent study of patients with community-acquired bloodstream infections found that 26.1% of patients  $\geq 85$  years of age had altered mental status compared with 14.3% of patients 65–84 years of age and 13.0% of patients  $<65$  years of age (28).

Fever, a classic sign of infection and one of the four SIRS criteria (Table 1), is less likely to develop in older patients with sepsis than in younger septic patients, but it remains a common symptom even among the oldest infected patients. In a classic geriatrics study, Gleckman and Hibert (31) found that 87% of older patients with bacteremia had fever compared with 96% of younger bacteremic patients. Among the older patients who do develop fever when infected, the temperature may not rise to the levels observed among younger patients. Nearly one-half of the older patients evaluated in a nursing home investigation had a blunted fever response to

infection (maximum temperature  $<101^{\circ}\text{F}$ ) (32). The low-grade fever that such patients develop, however, should be noticed by the careful clinician; one-fourth of the patients with blunted fevers in this study had significant changes in temperature but failed to reach  $101^{\circ}\text{F}$  because of a low baseline temperature. Thus, knowledge of an older person's baseline temperature may assist in early recognition of infection. In addition, older patients with acute infection should be carefully monitored for signs of systemic inflammatory response that indicate the development of sepsis.

### ***Microbiology and Source of Infection***

The etiology of sepsis varies with age in several ways. Gram-negative organisms, for example, are more frequently the source of infection in older patients compared with younger patients. Septic patients  $\geq 65$  years of age were 1.31 times more likely to have gram-negative infections than younger patients with sepsis in the large study by Martin et al. (3), and studies of bacteremia have yielded similar results. Diekema and colleagues (33) examined 25,745 episodes of community-acquired bacteremia from 1997 to 2000 and determined that *Escherichia coli* was the most frequently isolated pathogen among older patients, whereas *S. aureus* was the most frequently isolated pathogen among younger patients. When they do develop sepsis from a gram-positive organism, older patients are more likely to be infected with antibiotic-resistant organisms. At least two studies of *S. aureus* bacteremia found that infection with methicillin-resistant *S. aureus* was more common among older patients than younger patients (12, 23).

The microbiological differences of sepsis observed between older and younger patients can be explained by multiple factors, including age-related differences in source of infection, environmental exposure, and immune function. The genitourinary tract is the most common source of sepsis in older patients. Martin et al. (3) found that older patients were 1.38 times more likely than younger patients to have a genitourinary source of sepsis, and Lark and colleagues (34) observed that older patients were more likely than younger patients to have a genitourinary source of bacteremia. In fact, in another study of older patients with bloodstream infections, 34% of patients 60–79 years of age had genitourinary sources of infection and 50% of patients 80 years of age and older had genitourinary infections (35). Even among patients with the same source for sepsis, age-related differences in microbiology exist. In one large study, gram-negative organisms accounted for 34.1% of cases of sepsis in older patients arising from respiratory tract infections compared with 20.5% of cases in younger patients (3), a difference likely due to increased exposure to gram-negative organisms experienced by older patients. In a study by Valenti et al. (36), only 9% of independent residents living in apartments had oropharyngeal colonization with gram-negative bacilli, whereas 60% of patients on an acute hospital ward were colonized. Thus, because of the higher rate of comorbid illness and exposure to healthcare facilities, older patients are more frequently exposed to gram-negative organisms.

## Diagnostic Tests

No single test exists to accurately make the diagnosis of sepsis, and the syndrome is frequently overlooked in older patients. In a study of 238 episodes of bacteremia in patients  $\geq 65$  years of age, 75% of patients met the definition of sepsis, but only 11% of patients were admitted with a documented diagnosis of “sepsis” (37). Because atypical symptoms and signs are common among older patients with sepsis, clinicians must have a heightened suspicion for infection when evaluating acutely ill older patients with nonspecific symptoms; the presence of SIRS should prompt empirical sepsis management until infection has been excluded.

All that is necessary to make a diagnosis of sepsis – which, by definition, is a clinical diagnosis rather than a microbiologic one – in the setting of SIRS is a suspicion for infection. As soon as sepsis is considered, a thorough physical examination and microbiologic studies should be performed, if not already complete (Table 3). Blood cultures should be obtained from two different sites, and specimens should be obtained from potentially infected sites, either as samples of body fluids (e.g., sputum, urine, or cerebrospinal/peritoneal/pleural fluid) or of exudates (e.g., abscesses or purulent drainage), for cultures and smears (e.g., Gram or fungal stains).

**Table 3** Initial resuscitation and treatment of infection

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*Initial resuscitation (first 6 h)*

- Begin resuscitation immediately for patients in shock or with hypoperfusion (1C)<sup>a</sup>
- Target resuscitation goals (1C)
- Augment resuscitation with further fluid, packed red blood cells and/or dobutamine if goals are not achieved (2C)

*Diagnosis*

- Obtain appropriate cultures before starting antibiotics provided this does not significantly delay antimicrobial administration (1C)
- Perform imaging studies promptly (1C)

*Antibiotic therapy*

- Begin intravenous antibiotics as early as possible, within the first hour of recognizing severe sepsis (1D) and septic shock (1B)
- Use one or more broad-spectrum agents active against likely pathogens and with good penetration into presumed source (1B)
- Reassess antimicrobial regimen daily (1C)

*Source identification and control*

- A specific anatomic site of infection should be established as rapidly as possible (1C)
  - Formally evaluate patient for a focus of infection amenable to source control measures (e.g., abscess drainage, tissue debridement) (1C)
  - Implement source control measures as soon as possible following successful initial resuscitation (1C)
  - Remove intravascular access devices if potentially infected (1C)
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Adapted from Dellinger et al. (43)

<sup>a</sup>Grades recommendations are indicated in *parentheses*, with the *numbers* signifying the strength (1 = strong, 2 = weak) of the recommendation and the *letters* signifying the quality of the evidence (A randomized controlled trial; B downgrade randomized controlled trial or upgrade observational study; C well-done observational study; D case series or expert opinion)



Additionally, radiologic studies (e.g., chest radiographs, computed tomography scans of the chest or abdomen, ultrasound of the hepatobiliary tract, etc.) should be done to identify the source of infection. Detailed descriptions of these and other tests used to diagnose many of the specific infections that may cause sepsis are available throughout this book.

The diagnostic yield from such tests may be diminished by age-related factors. Sputum specimens from older patients, for example, may not meet the cytologic criteria for an adequate specimen because of inadequate cough or inability to participate in specimen collection due to impaired cognition. Delirium often develops in the setting of sepsis; older age is a risk factor for this neurologic complication that occurs in 10–30% of older patients admitted to the hospital (38) and up to 80% of those admitted to the intensive care unit (39). Diagnostic studies, including radiologic examinations and the collection of specimens, typically require patient cooperation, and delirium can significantly limit attempts to perform these studies. Even when tests can be performed, underlying comorbid disease that is common among elderly persons can complicate the interpretation of results. Chronic lung disease, malignancy, or heart failure, for example, may make it difficult to identify pneumonia on a chest radiograph.

Procalcitonin, a precursor peptide from the hormone calcitonin, becomes markedly elevated in the presence of infection and has been touted as indicator of sepsis that can be used when SIRS is recognized and there is uncertainty regarding the presence of infection. Because such circumstances occur frequently among older patients due to the often atypical symptoms manifest during infection, procalcitonin may have great utility in this population. Additional research is needed, however, before procalcitonin can be recommended as part of the routine approach to the diagnosis of sepsis in older patients, as recent studies have failed to confirm initially promising results (40).

## Treatment

Effective management of sepsis involves treatment of both the underlying infection and the inflammatory response. Additionally, supportive measures are often necessary because of the high incidence of organ failure associated with sepsis. The crucial role of antibiotics in the treatment of sepsis has been recognized for over half a century (41), but effective sepsis-specific treatments (i.e., measures intended to quell the systemic response of sepsis) have not been available until recently.

To help improve the management, diagnosis, and treatment of sepsis, an international collaboration of critical care and infectious disease experts – known as the Surviving Sepsis Campaign – developed clinical guidelines for the management of severe sepsis and septic shock (42). With the support of numerous international medical societies (no industry funding supported the guidelines revision process), the guidelines were revised in 2006/2007 to reflect the latest research findings (43); the revised guidelines are summarized in Tables 3–5. Though most of these guide-

**Table 4** Hemodynamic support and adjunctive therapy*Fluid therapy*

- Fluid-resuscitate using crystalloids or colloids (1B), targeting a CVP of  $\geq 8$  mm Hg ( $\geq 12$  mmHg if mechanically ventilated) (1C)<sup>a</sup>
- Give fluid challenges of 1,000 mL of crystalloids or 300–500 mL of colloids over 30 min (1D)
- Rate of fluid administration should be reduced if cardiac filling pressures increase without concurrent hemodynamic improvement (1D)

*Vasopressors*

- Maintain MAP  $\geq 65$  mmHg (1C)
- Norepinephrine and dopamine centrally administered are the initial vasopressors of choice (1C)
- Vasopressin 0.03 units/min may be subsequently added to norepinephrine with anticipation of an effect equivalent to norepinephrine alone (2C)
- Use epinephrine as the first alternative agent in septic shock when blood pressure is poorly responsive to norepinephrine or dopamine (2B)
- In patients requiring vasopressors, insert an arterial catheter as soon as practical (1D)

*Inotropic therapy*

- Use dobutamine in patients with myocardial dysfunction (1C)

*Corticosteroids*

- Consider intravenous hydrocortisone for adult septic shock when hypotension responds poorly to adequate fluid resuscitation and vasopressors (2C)
- Steroid therapy may be weaned once vasopressors are no longer required (2D)

*Recombinant human activated protein C*

- Consider rhAPC in adult patients with sepsis-induced organ dysfunction with clinical assessment of high risk of death (typically APACHE II  $\geq 25$  or multiple organ failure) if there are no contraindications (2B, 2C for postoperative patients)
- Adult patients with severe sepsis and low risk of death (typically, APACHE II  $< 20$  or one organ failure) should not receive rhAPC (1A)

*Abbreviations:* CVP central venous pressure; MAP mean arterial pressure; rhAPC recombinant human activated protein C; APACHE acute physiology and chronic health evaluation

Adapted from Dellinger et al. (43)

<sup>a</sup>Grades recommendations are indicated in *parentheses*, with the *numbers* signifying the strength (1 = strong, 2 = weak) of the recommendation and the *letters* signifying the quality of the evidence (A randomized controlled trial; B downgrade randomized controlled trial or upgrade observational study; C well-done observational study; D case series or expert opinion)

lines should be employed in the management of both older and younger patients with sepsis, some age-related considerations warrant comment.

## ***Antimicrobial Treatment and Source Control***

Two priorities that guide the use of antibiotics when treating sepsis are the need for rapid administration and for broad empirical coverage. Thus, intravenous antibiotics should be initiated as quickly as possible after appropriate specimens for cultures have been obtained; antibiotics should always be started within 1 h of recognizing septic shock or severe sepsis (44), even if specimen collection is

**Table 5** Other supportive therapy*Blood product administration*

- Give red blood cells when hemoglobin decreases to <7.0 g/dL (<70 g/L) to target a hemoglobin of 7.0–9.0 g/dL in adults (1B).<sup>a</sup> A higher hemoglobin level may be required in special circumstances (e.g., myocardial ischemia, severe hypoxemia, acute hemorrhage, cyanotic heart disease, or lactic acidosis)

*Mechanical ventilation of sepsis-induced ALI/ARDS*

- Target a tidal volume of 6 mL/kg (predicted) body weight in patients with ALI/ARDS (1B)
- Target an initial upper limit plateau pressure ≤30 cm H<sub>2</sub>O (1C)
- Maintain mechanically ventilated patients in a semirecumbent position (head of the bed raised to 45°) unless contraindicated (1B), between 30° and 45° (2C)
- Use a weaning protocol and an SBT regularly to evaluate the potential for discontinuing mechanical ventilation (1A)
- Use a conservative fluid strategy for patients with established ALI who do not have evidence of tissue hypoperfusion (1C)

*Sedation, analgesia, and neuromuscular blockade in sepsis*

- Use sedation protocols with a sedation goal for critically ill mechanically ventilated patients (1B)
- Use either intermittent bolus sedation or continuous infusion sedation to predetermined end points (sedation scales), with daily interruption/lightening to produce awakening. Retitrate if necessary (1B)

*Glucose control*

- Use intravenous insulin to control hyperglycemia in patients with severe sepsis following stabilization in the ICU (1B), aiming to keep blood glucose <150 mg/dL (8.3 mmol/L) using a validated protocol for insulin dose adjustment (2C)

*Deep vein thrombosis prophylaxis*

- Use either low-dose UFH or LMWH, unless contraindicated (1A)
- Use a mechanical prophylactic device, such as compression stockings or an intermittent compression device, when heparin is contraindicated (1A)

*Stress ulcer prophylaxis*

- Provide stress ulcer prophylaxis using H<sub>2</sub> blocker (1A) or proton pump inhibitor (1B)

*Consideration for limitation of support*

- Discuss advance care planning with patients and families. Describe likely outcomes and set realistic expectations (1D)

*Abbreviations:* ALI acute lung injury; ARDS acute respiratory distress syndrome; SBT spontaneous breathing trial; UFH unfractionated heparin; LMWH low-molecular weight heparin

Adapted from Dellinger et al. (43)

<sup>a</sup>Grades recommendations are indicated in *parentheses*, with the *numbers* signifying the strength (1 = strong, 2 = weak) of the recommendation and the *letters* signifying the quality of the evidence (A randomized controlled trial; B downgrade randomized controlled trial or upgrade observational study; C well-done observational study; D case series or expert opinion)

delayed (Table 3). Since inadequate initial therapy results in increased mortality, initial empirical therapy should be selected such that activity against all likely pathogens is achieved (13).

Though these and other essential principles of antimicrobial use pertain to all age groups, age-related differences in comorbid conditions as well as pharmacokinetic and pharmacodynamic parameters must be considered when treating older patients with antibiotics (see also the chapter “Principles of Antimicrobial Therapy”). Briefly, antibiotics should be selected according to the patient’s risk for severe infections and multidrug-resistant pathogens based on lifestyle (e.g., place

of residence, recent hospitalization, etc.), they should be selected to avoid severe drug-drug interactions based on a complete medication history, and they should be dosed to account for age-related and comorbidity-induced changes in renal and hepatic function. Because of the higher risk of adverse effects experienced by older persons receiving antibiotics, clinicians must be familiar with possible side effects and monitor for them carefully.

All patients should be evaluated for a focus of infection amenable to source control measures (e.g., drainage of an abscess, debridement of necrotic tissue, or removal of a device), and this evaluation should be conducted as quickly as possible (Table 3). When source control is required, options that result in the least physiologic insult should be pursued, especially in older patients with multiple comorbidities.

### ***Hemodynamic Support***

All patients with sepsis should be monitored carefully for evidence of tissue hypoperfusion (e.g., hypotension, elevated lactate, or organ dysfunction), which should prompt immediate goal-directed resuscitation (Table 3). A protocol of early goal-directed therapy improved survival in a randomized trial of 263 patients with sepsis (average age, 66 years) that evaluated the efficacy of a protocol that used central venous pressure, mean arterial pressure, and central venous oxygen saturation to guide resuscitation (45). Either colloids or crystalloids can be used during resuscitation, and fluid challenges are recommended initially (e.g.,  $\geq 1,000$  mL of crystalloids or 300–500 mL of colloids over 30 min) (Table 4). Though older patients with poor cardiac compliance may develop pulmonary edema as a result of excess fluid accumulation, the increased capacitance of the vasculature resulting in septic shock makes overresuscitation less of a danger than underresuscitation.

Vasopressors should be started (either norepinephrine or dopamine) if initial fluid resuscitation does not result in improvement such that mean arterial pressure is maintained  $\geq 65$  mmHg (Table 4). Though there is no evidence to support its use alone, vasopressin at 0.03 units/min should be considered in combination with norepinephrine (10). Additionally, dobutamine should be administered if myocardial dysfunction is suggested by elevated cardiac filling pressures and low cardiac output (Table 4).

### ***Adjunctive Sepsis-Specific Therapies***

Patients who remain in shock, despite adequate fluid resuscitation and vasopressor administration, are at very high risk of death and may respond to treatment with intravenous hydrocortisone, which should be given in doses  $<300$  mg daily and weaned when vasopressors are no longer necessary (Table 4). This recommendation

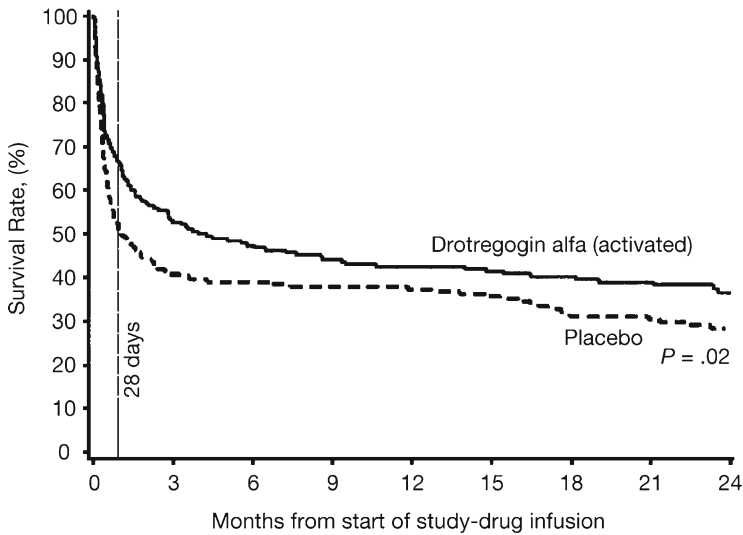
remains controversial because of inconsistent research results. In a randomized trial by Annane et al. (46) that enrolled 300 patients (mean age, 61 years) with persistent septic shock unresponsive to vasopressor therapy, treatment with low doses of hydrocortisone and fludrocortisone significantly improved 28-day survival. Recently, however, an international trial that enrolled 499 patients with septic shock (mean age, 63 years) regardless of how blood pressure responded to vasopressors determined that low-dose hydrocortisone did not improve overall survival (47). Additionally, several large clinical trials previously found that high-dose corticosteroids, which can result in immunosuppression, hyperglycemia, poor wound healing, delirium, and myoneuropathy, are ineffective or harmful in the treatment of sepsis.

After antibiotics and resuscitation have been initiated to patients with severe sepsis, recombinant human activated protein C (rhAPC, drotrecogin alfa (activated)) should be considered for administration to those with high risk of death (e.g., Acute Physiology and Chronic Health Evaluation (APACHE) II  $\geq 25$  or multiple organ failure) and no contraindications (Table 4), though considerable controversy remains among infectious disease specialists regarding the efficacy of this treatment. The drug should not be administered to patients with active internal bleeding, intracranial neoplasm, or evidence of cerebral herniation or mass lesion, known hypersensitivity to drotrecogin alfa (activated), hemorrhagic stroke within 3 months, recent intracranial or intraspinal surgery, severe head trauma within 2 months, presence of an epidural catheter, or trauma with an increased risk of life-threatening bleeding. Additionally, the drug should be cautiously considered if other bleeding risks are noted.

In an international, randomized, double-blind, placebo-controlled trial, treatment with rhAPC resulted in a 6.1% reduction in the absolute risk of 28-day mortality (9). The efficacy and safety of rhAPC among older patients (386 patients who were  $\geq 75$  years of age) was determined in a planned subgroup analysis, which found that treatment with rhAPC resulted in a 15.5% reduction in the absolute risk of 28-day mortality (Fig. 3) (20). Thus, these data suggest that older septic patients benefit as much as or more than younger patients from treatment with rhAPC. Also, older treated patients were not more likely than younger treated patients to experience serious bleeding; 3.9% of older patients on rhAPC had a serious bleeding event compared with 3.4% of younger patients on rhAPC. Serious bleeding rates among older and younger patients on placebo were 2.2 and 2.0%, respectively.

### ***Other Supportive Therapies***

Due to complications of sepsis, a large percentage of older patients with sepsis require numerous supportive therapies. The management of anemia, respiratory failure, and renal failure as well as the prevention of additional complications (e.g., deep vein thrombosis (DVT) and gastrointestinal stress ulcers), should be conducted in an evidence-based fashion as described in the Surviving Sepsis Campaign guidelines (Table 5).



**Fig. 3** Twenty-four-month Kaplan–Meier survival curves for patients  $\geq 75$  years of age enrolled in PROWESS, according to treatment group. Patients aged  $\geq 75$  years treated with drotrecogin alfa (activated) had significantly higher survival rates sustained throughout the 2-year follow-up period, compared with older patients treated with placebo ( $p = 0.02$ ). Figure from Ely et al. (20) with permission

Except for older patients with coronary artery disease and likely myocardial ischemia, supportive care for the anemia that frequently complicates sepsis should consist of a conservative transfusion strategy (Table 5); red blood cells should be transfused to maintain a hemoglobin of 7.0–9.0 g/dL based on a trial by Hebert et al. (48), which found that such a strategy was equivalent in outcomes to a more liberal approach that targeted a hemoglobin of 10 g/dL. Coronary artery disease is common, however, among older patients, and Wu and colleagues (49) determined that older patients admitted with myocardial infarction benefited from transfusions if their hemoglobin fell below 11 g/dL. Thus, older septic patients should be transfused liberally if active coronary ischemia is suspected.

All septic patients with respiratory failure requiring mechanical ventilation should be treated with a lung protective strategy consisting of low tidal volumes ( $\leq 6$  mL/kg of predicted body weight) and plateau pressures ( $\leq 30$  cm H<sub>2</sub>O) (Table 5). This strategy resulted in an 8.8% absolute reduction in 28-day mortality in a large, randomized controlled trial of patients with the acute respiratory distress syndrome (ARDS),  $>60\%$  of whom had severe sepsis (i.e., pneumonia or other sepsis with respiratory failure) (50). A similar benefit was observed among the 173 patients  $\geq 70$  years of age enrolled in this trial; low tidal volume ventilation resulted in a 9.9% absolute reduction in 28-day mortality in the older subgroup (51).

Whereas the method of full ventilatory support can significantly impact outcomes for septic patients with respiratory failure, the approach to discontinuation of ventilatory support as well as sedation (administered to nearly all mechanically

ventilated patients) can also affect outcomes. Older mechanically ventilated patients with sepsis, therefore, should be managed with a ventilator weaning protocol that includes regular spontaneous breathing trials (SBTs) (52) as well as a sedation protocol that includes use of a sedation scale, sedation goals, and daily interruption of sedatives (53) (Table 5). A recent randomized trial compared the efficacy of a paired sedation and ventilator weaning protocol among 335 mechanically ventilated medical intensive care unit (ICU) patients, the majority of whom had sepsis and/or ARDS (54), and found that the “wake up and breathe” protocol significantly increased time spent breathing without assistance as well as 1-year survival.

A number of other interventions are recommended during the supportive care of patients with sepsis, all of which are warranted when treating older septic patients. These include control of hyperglycemia and prevention of deep vein thrombosis and gastrointestinal stress ulcers (Table 5). One recent study found that when these and other therapies outlined herein are implemented together as a sepsis “bundle,” older patients with septic shock had improved outcomes (55).

In addition to the thoughtful treatment of older patients to prevent adverse outcomes, clinicians must be prepared and equipped to withhold life-sustaining treatment and provide quality end-of-life care when appropriate. The patient, when possible, and his or her family should be informed about the likely burden of treatment as well as the possible outcomes and the likelihood of these outcomes, because these factors strongly influence patients’ treatment preferences (56).

## Prevention

Currently, the only effective approach to the prevention of sepsis is to avoid infection, and methods for the prevention of many of the common infections that afflict older patients are described throughout this book.

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# Bronchitis and Pneumonia

Manisha Juthani-Mehta, MD and Vincent Quagliarello, MD

## Key Points

- The incidence, morbidity, and mortality of both bronchitis and pneumonia are high in older adults and increase with age.
- The clinical manifestations of bronchitis and pneumonia in older adults may not be typical (e.g., cough, fever, dyspnea). Many older adults, particularly nursing home residents, may present with altered mental status and with or without fever. Obtaining a chest X-ray is often critical to make the distinction between the two clinical entities.
- Unique risk factors for pneumonia in older adults include multiple comorbidities (e.g., COPD, DM, CHF), poor oral hygiene, lack of vaccinations (e.g., *S. pneumoniae*, influenza), and swallowing difficulty.
- Empirical treatment decisions for pneumonia should be based on site of care. Recent information suggests that in-home therapy for community dwellers and therapy within the nursing home for long-term care residents is feasible with good outcomes in selected patients.
- Prevention strategies for pneumonia should be targeted towards providing vaccinations, improving oral hygiene, and improving swallowing difficulty.

## Bronchitis

### *Epidemiology and Clinical Relevance*

Chronic bronchitis, which affects most patients with chronic obstructive pulmonary disease (COPD), is characterized by a chronic cough productive of sputum lasting

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more than 3 months of the year for 2 consecutive years. Chronic bronchitis usually results from smoking-related obstructive disease. Although many elderly patients with chronic bronchitis may be ex-smokers, age-related decline in lung function can also precipitate COPD symptoms. In elderly patients with chronic bronchitis, acute exacerbations of chronic bronchitis (AECB) are common. AECB is defined as worsening shortness of breath and cough and/or sputum production that cannot be accounted for by daily variability and requires a change in therapy. AECB can lead to poor quality of life, loss of functional status, hospitalizations, loss of lung function, and more often fatality in elderly patients. Risk factors for AECB include respiratory infection, environmental exposures (e.g., air pollution), and poor compliance with prescribed COPD therapies. Lower respiratory tract infection often triggers AECB accounting for 80% of all episodes. Viral infections, including influenza, parainfluenza, and rhinoviruses, account for 30% of exacerbations and are associated with superimposed bacterial infections as well. *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* are the most common pathogens in mild cases of AECB and account for 40–60% of cases. In more severe cases of AECB requiring mechanical ventilation, enteric gram-negative bacilli including *Pseudomonas* and *Stenotrophomonas* spp. have been identified. Atypical pathogens, mostly *Chlamydia pneumoniae*, have only been implicated in <10% of cases (1).

### ***Clinical Manifestations***

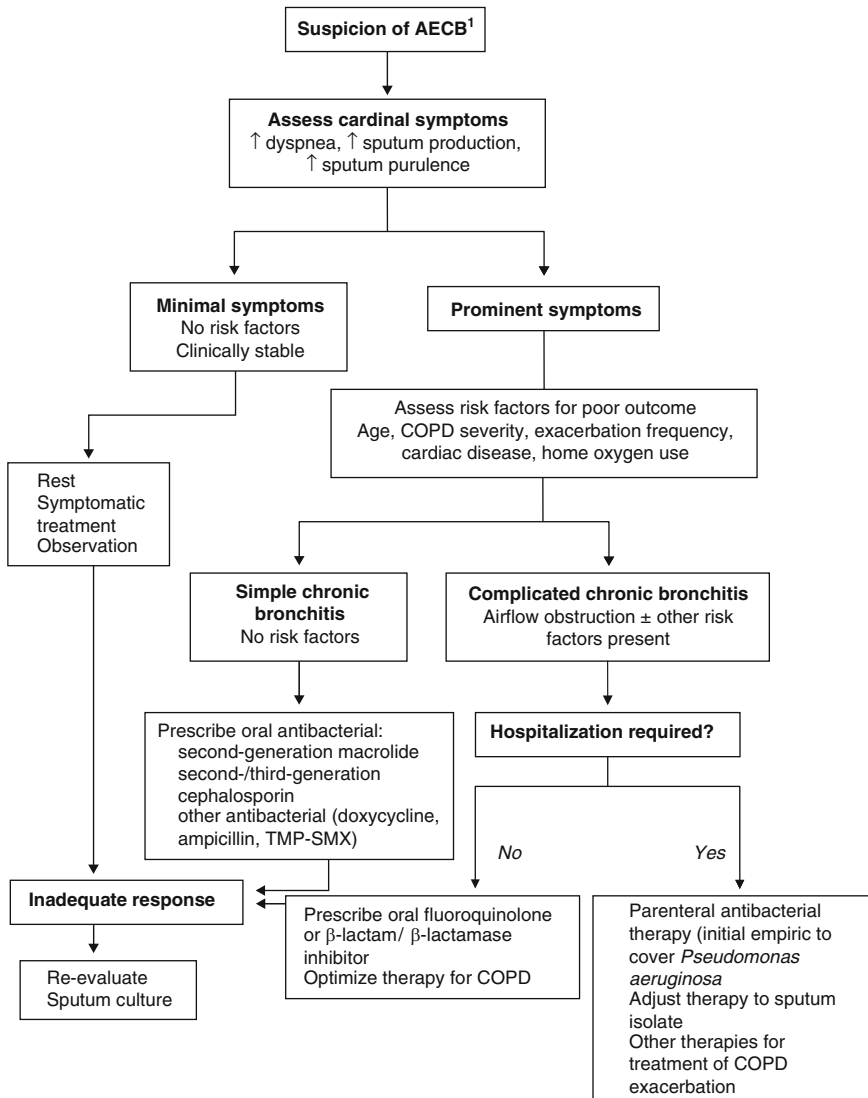
In elderly patients, symptoms and signs of AECB include increased sputum production and/or sputum purulence, worsening dyspnea and cough, onset of or worsened fluid retention, fever, tachycardia, and altered mental status. Increasing age and comorbid conditions such as cardiac disease, malnutrition, and underlying severe COPD increases the risk of hospitalization and treatment failure (1).

### ***Diagnostic Tests***

The diagnosis of AECB is often made on clinical findings. However, if there is sufficient sputum production, a sputum specimen for Gram stain and culture can help guide antimicrobial treatment decisions. In elderly patients, where symptoms of AECB may be present but sputum often cannot be produced, empirical treatment should be initiated. A chest radiograph should be obtained, especially if there are abnormal breath sounds to differentiate AECB from pneumonia.

### ***Treatment***

The main goal of treating AECB is to allow for rapid symptom relief, eradication of causative pathogens, decreased likelihood of future recurrence, and preservation



**Fig. 1** Algorithm for treatment of acute exacerbations of chronic bronchitis<sup>1</sup>  
 COPD = chronic obstructive pulmonary disease  
 TMP-SMX = trimethoprim–sulfamethoxazole

of lung function. Early studies of effectiveness of antibacterials as treatment for AECB were inconclusive; however, more recent clinical trials have shown that antimicrobial therapy is effective when administered to risk-stratified groups. An algorithm for empirical treatment decisions in elderly patients with AECB is provided in Fig. 1. Because renal clearance may decline for certain antibiotics with age, some elderly patients may need to be treated as if they have chronic renal insufficiency. Other therapeutic interventions include supplemental oxygen if needed, bronchodilators, rest, fluids, optimized nutrition, judicious use of corticosteroids, early

administration of a neuraminidase inhibitor if influenza infection is confirmed, and treatment of right heart failure if present (1).

## ***Prevention***

Pulmonary rehabilitation programs can improve the baseline lung function of elderly patients with chronic bronchitis thereby preventing future episodes. Smoking cessation is critical and can also lead to the attenuation of disease progression. Pneumococcal and influenza vaccines are often administered to prevent both upper and lower respiratory tract infection (1). Further details on vaccinations are presented in the section on Pneumonia Prevention.

## **Pneumonia**

### ***Epidemiology and Clinical Relevance***

#### **Epidemiology and Classification**

Pneumonia is a leading cause of morbidity and mortality in older adults; the incidence of pneumonia increases with age (2). Almost half of all infectious diseases hospitalizations and deaths are associated with pneumonia in older adults (3). While rates for those aged  $\geq 85$  years have remained consistently high, rates of hospitalization for pneumonia among older adults aged 65–84 have increased over time (4). The overall rate of community-acquired pneumonia (CAP) in persons aged 65–69 years ranges from 18.2 cases per 1,000 person-years to 52.3 cases per 1,000 person-years among those aged  $\geq 85$  years, resulting in an estimate of 915,900 episodes per year of CAP in adults  $\geq 65$  years in the United States (2). For residents of nursing homes age 65 years and older, the rate of nursing home acquired pneumonia (NHAP) is as high as 365 cases per 1,000 person-years (5). Pneumonia is classified into four categories: community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP), nursing home acquired pneumonia (NHAP) or health-care-associated pneumonia (HCAP), and ventilator-associated pneumonia (VAP). CAP and HAP are differentiated as pneumonia that develops while a patient is in an outpatient or inpatient setting, respectively. VAP is defined as pneumonia arising after the patient has received at least 24 h of mechanical ventilation. NHAP occurs in nursing home residents that acquire pneumonia while residing in the nursing home. Since an increasing number of patients, especially elderly patients, utilize rehabilitation facilities, outpatient surgical centers, and dialysis centers, pneumonia acquired by patients utilizing these facilities is considered HCAP. The epidemiology of HCAP more closely resembles HAP since these patients are not truly residing in the “community” (6).

## Risk Factors

For CAP among seniors, age, male sex, COPD, immunosuppression, smoking, cancer, and previous hospitalizations for pneumonia were identified as risk factors (2). Functional status at the time of hospital admission has been shown to be a powerful predictor of mortality (7). Among nursing home residents, inadequate oral care, swallowing difficulty, and lack of influenza vaccine have been shown to be modifiable risk factors for NHAP (5, 8). Malnutrition has also been implicated as a potential risk factor for pneumonia in nursing home residents (9). Specifically, nursing home residents with low serum zinc concentrations had an increased incidence and duration of pneumonia, an increased number of new antibiotic prescriptions, and more days of antibiotic use than residents with normal serum zinc concentrations (10).

## Microbiology

The common etiologies for pneumonia in older adults are dependent on the site of acquisition. The predominant pathogen in seniors in all sites is *Streptococcus pneumoniae* (11). For CAP that often can be treated in the outpatient setting, the common pathogens include *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, *Haemophilus influenzae*, *Chlamydia pneumoniae* and the respiratory viruses (e. g., Influenza A and B, adenovirus, respiratory syncytial virus (RSV), parainfluenza, and human metapneumovirus). *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* are common causes of CAP in younger adults, but it is unknown how prevalent these pathogens are in the elderly. When the severity of CAP is greater and requires inpatient therapy, the above listed pathogens, *Legionella* species and *Staphylococcus aureus* secondary infection during influenza pneumonia, should be considered (12). For patients with HCAP, *Staphylococcus aureus* (both methicillin-susceptible and methicillin-resistant) was identified in a large proportion of patients (6). Gram-negative bacteria pneumonia (e.g., *Pseudomonas* species, *Klebsiella* species) is more common in HAP, NHAP, VAP, and in community-dwelling older adults with preexisting lung disease, particularly those with high aspiration risk. In outbreak settings, *Legionella pneumophila*, *Chlamydia pneumoniae*, RSV, influenza, and parainfluenza should be strongly considered (11).

Other pathogens to consider in older adults include mycobacterial diseases. Reactivation of *Mycobacterium tuberculosis* is three to four times higher in nursing home residents than in community dwellers. *Mycobacterium avium intracellulare* complex is the causative agent in many evolving, destructive pulmonary infections often in nonsmoking older women who present with cough, fatigue, fever, weight loss, and nonspecific pulmonary infiltrates. Human immunodeficiency virus (HIV) infection with opportunistic pulmonary infections such as *Pneumocystis jirovecii* (formerly known as *carinii*) pneumonia, tuberculosis, cryptococcosis, have been increasingly reported in older adults. With advances in highly active antiretroviral therapy, HIV-infected individuals are living longer, but now older adults often

develop opportunistic pulmonary infections that are associated with HIV treatment failure (see also Chapter “Human Immunodeficiency Virus/Acquired Immuno-deficiency Syndrome”). Other opportunistic infections such as *Nocardia asteroides* and pulmonary aspergillosis should be considered in older adults with malnutrition, progressive weight loss, and evolving pulmonary infiltrates (11).

## ***Clinical Manifestations***

### **Pathophysiology**

The primary mechanism of pneumonia, for both CAP and NHAP, is bronchoaspiration. Approximately half of all healthy adults aspirate small amounts of oropharyngeal secretions during sleep. Since most healthy adults are colonized with few virulent pathogens in their oropharynx and since forceful coughing, intact ciliary transport, and normal humoral and cellular immune mechanisms are present, healthy adults are often protected from repeated episodes of pneumonia. However, in older adults, there is a higher frequency of silent aspiration, particularly in those with dementia and stroke. Physiologic changes such as a decrease in elastic recoil of the lung, a decrease in compliance of the chest wall, a decrease in respiratory muscle strength, calcification within the rib cage, osteoporosis and resultant vertebral fractures, decreased mucociliary clearance rates, and swallowing difficulty are all associated with aging. In addition, older adults tend to be colonized in the upper respiratory tract with more virulent pathogens such as Enterobacteriaceae, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* (11). The combination of higher rates of aspiration, impaired airway defense mechanisms, and colonization with more pathogenic organisms make older adults at greater risk for the development of pneumonia.

During pneumonia, acute inflammation is characterized by an accumulation of neutrophils and plasma exudate in alveolar spaces. In pulmonary capillaries of uninfected lungs, neutrophils remain trapped and ready to respond when needed. During pulmonary infection, neutrophils migrate into alveolar spaces and kill microbes primarily through phagocytosis. Many plasma proteins present in exudates serve opsonic, bacteriostatic, and microbicidal functions as well during infection. As critical as inflammation is for innate immunity and host defense, it can also directly injure the lungs resulting in acute lung injury (13). In older adults, the inflammatory response itself elicited by highly pathogenic organisms can add to the severity of disease experienced in this population.

### **Clinical Features**

Cough, sputum production, chills, and pleuritic chest pain are more commonly seen among patients with CAP; elderly nursing home residents with NHAP often present



with altered mental status and with or without fever. The classic triad of cough, fever, and dyspnea is seen in about 50% of older patients with CAP. Tachypnea (respiratory rate > 20 breaths/min) and tachycardia (heart rate > 100 beats/min) were seen in two-thirds of elderly patients with pneumonia, and these signs may precede other clinical features by 3–4 days. Many elderly patients, particularly those that are chronically debilitated, may present with very subtle clinical manifestations such as an aggravation of preexisting comorbidities (e.g., diabetes, CHF), unexplained falls, failure to thrive, and poor appetite (11). In older patients, *L. pneumophila* is a frequent cause of an atypical pneumonia syndrome presenting with constitutional symptoms myalgias, diarrhea, altered mental status, bradycardia, and hyponatremia. None of these signs or symptoms is specific for *L. pneumophila*, but they can provide insight into the causative pathogen (11).

### **Diagnostic Tests**

The diagnosis of CAP is made by having suggestive clinical features (e.g., cough, fever, sputum production, and pleuritic chest pain) with a demonstrable infiltrate on chest radiograph. Physical examination findings (e.g., bronchial breath sounds, rales) are important but less sensitive and specific than chest radiograph findings. Older adults may lack clinical features and/or physical examination findings. Therefore, a chest radiograph is important to differentiate CAP from acute bronchitis in an older adult. Routine diagnostic tests to identify an etiologic agent are optional for outpatients with CAP since most patients do well with empirical antibiotic therapy. Pretreatment blood cultures and an expectorated sputum specimen for Gram stain and culture are standard samples to obtain. However, pretreatment blood cultures only identified a probable pathogen in 5–14% of patients with CAP. Yield from blood cultures is highest in patients with severe CAP, in which more pathogenic organisms, such as *S. aureus*, *P. aeruginosa*, and other gram-negative bacilli are identified (12). Since these pathogens are more commonly identified in older adults, blood cultures should be part of the standard diagnostic evaluation of an older adult with CAP. The clinical indications for more extensive etiologic diagnostic testing are listed in Table 1. Many diagnostic tests to determine the etiology of pneumonia require sputum production, and often older adults have difficulty producing sputum. Nevertheless, diagnostic testing is particularly important when results may alter antibiotic management decisions, when outbreaks must be identified (e.g., severe acute respiratory syndrome [SARS], influenza, Legionnaire's disease, agents of bioterrorism), and when there are epidemiologic implications (e.g., emergence of resistant pathogens). The clinical utility of sputum culture results is largely dependent on the quality of the sputum specimen and whether the specimen was obtained prior to antimicrobial therapy. When sputum is difficult to obtain, urinary antigen tests for *S. pneumoniae* and *L. pneumophila* serogroup 1 can assist in making a diagnosis. These tests have a higher diagnostic yield in patients with the most severe disease. Other advantages of these tests include rapidity of results, ability to detect

**Table 1** Community-acquired pneumonia: clinical indications for more extensive diagnostic testing<sup>12</sup>

Indication	Blood culture	Sputum culture	<i>Legionella</i> UAT	Pneumococcal UAT	Other
Intensive care unit admission	X	X	X	X	X <sup>a</sup>
Failure of outpatient antibiotic therapy		X	X	X	
Cavitary infiltrates	X	X			X <sup>b</sup>
Leukopenia	X			X	
Active alcohol abuse	X	X	X	X	
Chronic severe liver disease	X			X	
Severe obstructive/structural lung disease		X			
Asplenia	X			X	
Recent travel (past 2 weeks)			X		X <sup>c</sup>
Positive <i>Legionella</i> UAT result		X <sup>d</sup>	NA		
Positive Pneumococcal UAT result	X	X		NA	
Pleural effusion	X	X	X	X	X <sup>e</sup>

<sup>12</sup>Reference 12

NA not applicable; UAT urinary antigen test

<sup>a</sup>Endotracheal aspirate if intubated, possibly bronchoscopy or nonbronchoscopic bronchoalveolar lavage.<sup>b</sup>Fungal and tuberculosis cultures<sup>c</sup>Specific tests for exposure to unique pathogens (e.g., avian influenza, SARS, *Hantavirus*, *Burkholderia pseudomallei*)<sup>d</sup>Special media for *Legionella*<sup>e</sup>Thoracentesis and pleural fluid cultures

antigen even after initiation of antibiotic therapy, and high specificity. For *Legionella*, all commercially available urinary antigen assays only detect serogroup 1. Although serogroup 1 accounts for 80–95% of community-acquired cases of Legionnaire's disease, other serogroups would not be detected by the standard urinary antigen assay (12). For influenza A and B, adenovirus, RSV, parainfluenza, and human metapneumovirus, a direct fluorescent antibody test can be performed rapidly on nasopharyngeal samples and can assist in determining whether antiviral or antimicrobial therapy is warranted. For patients with HAP that require mechanical ventilation, postintubation tracheal aspiration has been shown to be reliable for microbiologic diagnosis when compared with bronchoalveolar lavage (BAL), plugged telescoping catheter, and protected specimen brush procedures (14).

## Treatment

### Predicting Clinical Outcome

Particularly in older adults, prognostic scoring systems can help predict outcomes of therapy. Most scoring systems predict mortality; however, few assess other clinical outcomes such as physical functional ability, cognitive ability, need for nursing home

care, and overall quality of life which are important outcomes for older adults (15). The pneumonia severity index (PSI) derived and validated by Fine et al. is a two-step 20 variable scoring system that is best at identifying patients that can be treated as outpatients. However, many older adults fall into the high-risk groups purely based on their age; therefore, it is not as useful at predicting treatment outcomes in this group of patients (15). Lim et al. derived and validated CURB65, a modified version of the scoring system of the British Thoracic Society. This system consists of five parameters: confusion, uremia, respiratory rate, low blood pressure, and age  $\geq 65$  years (16). CURB65 has been shown to be useful in the emergency department because of its simplicity of use and ability to identify low-risk patients (17). Modifications to CURB65 to account for age  $\geq 85$  years and higher blood urea levels further identify those of the older cohort with severe pneumonia (18). In one scoring system derived and validated among seniors  $\geq 65$  years of age, five features were independently predictive of hospital mortality: age  $> 85$  years, impaired motor response, creatinine level of  $> 1.5$  mg/dL, presence of coexisting disease, and extremely abnormal vital signs (19). In all of these scoring systems, age  $> 85$  years has been shown to be the greatest predictor of mortality. Currently, no scoring systems exist that predict outcomes other than mortality in the care of older adults with pneumonia but several observational studies in nursing home populations document a decline in function after pneumonia. In a prospective study of nursing home residents with lower respiratory tract infection, the incidence in decline of functional status was 29%. Those that had a decline in functional status at 30 days after pneumonia episode were less likely to recover to their baseline status at 90 days (20). Similarly, in a large prospective trial of older adults, functional decline occurred more rapidly among subjects who developed infection and there was a dose response with an increased risk of decline as the number of infectious episodes increased (20).

## Site of Care

Prognostic scoring systems, particularly CURB-65, may help easily identify those patients that can be treated as outpatients. However, for patients with CURB-65 scores  $\geq 2$ , hospitalization or intensive in-home health care services are usually warranted. Patients with septic shock requiring vasopressors or with acute respiratory failure requiring intubation and mechanical ventilation are usually directed to admission in the intensive care unit (12). However, among older adults, assessing goals of care are often warranted before initiating hospital and/or intensive care unit (ICU admission). For patients with CAP, hospital-at-home services have been shown to be feasible, safe, efficacious, and more cost effective than hospital admission (21). In addition, hospital-at-home has been associated with lower levels of family member stress and does not appear to shift the burden of care from hospital staff to family members (22). ICU admission is not warranted in the older adult in whom comfort is the main goal of care. For nursing home residents with NHAP, a randomized controlled trial of a clinical pathway for treatment of NHAP in the nursing home versus hospitalization resulted in comparable clinical outcomes,

while reducing hospitalizations and health care costs. In the clinical pathway group, 34 of 327 (10%) were hospitalized while 76 of 353 (22%) were hospitalized in the usual care group, resulting in greater than 50% proportional reduction in hospitalizations. The mortality rate was 8% (24 deaths) in the clinical pathway group versus 9% (32 deaths) in the usual care group. There were no significant differences in quality of life or functional status between the two groups. The overall cost savings by utilizing the clinical pathway per resident was \$1,016 (95% CI, \$207–\$1,824) (23). Although this study demonstrated that treatment of pneumonia in the nursing home can reduce hospitalizations and cost, only those residents that met each of the following criteria could be treated in the nursing home for study purposes: pulse of 100/min or less, respiratory rate of less than 30/min, systolic blood pressure of at least 90 mm Hg, oxygen saturation of at least 92% (or  $\geq 90\%$  if the resident had COPD), and the ability to eat and drink. If any one of these criteria was not met, the resident was transferred to the hospital (23). Additionally, because this study was conducted in Canada, and since the United States has a different healthcare financing system, generalizing this clinical pathway to treat pneumonia in the nursing home may not be feasible in the United States. Nevertheless, this study demonstrated proof of principle, and this approach warrants consideration in residents with mild to moderate pneumonia.

### Empirical Antibiotic Therapy

For healthy older adults with no comorbidities, empirical treatment of outpatient CAP can be initiated with a macrolide or doxycycline. However, for those seniors with comorbidities such as chronic heart, lung, liver, or renal disease, diabetes mellitus, alcoholism, or immunosuppression, a respiratory quinolone (e.g., moxifloxacin, levofloxacin) or a  $\beta$ -lactam plus a macrolide should be initiated for outpatient or inpatient CAP treatment. Retrospective data suggest that patients with severe CAP treated with a  $\beta$ -lactam plus a macrolide may have improved clinical outcomes compared with those patients treated with a respiratory quinolone (24). If *Pseudomonas aeruginosa* is a concern, an antipneumococcal, antipseudomonal  $\beta$ -lactam (e.g., piperacillin-tazobactam, cefepime, imipenem, meropenem) should be considered. Double coverage with ciprofloxacin or levofloxacin can be considered as well. Aminoglycosides are often recommended for double coverage of *Pseudomonas*; however, in older adults with a decreased glomerular filtration rate, aminoglycosides should be administered cautiously because of nephrotoxic effects. If community-acquired MRSA is a consideration, vancomycin or linezolid can be added (12).

For nursing home residents or older adults with HAP, HCAP, or VAP, antipseudomonal coverage and MRSA coverage may be warranted empirically. Therefore, a common empirical regimen for treatment of HAP, HCAP, or VAP is piperacillin-tazobactam and vancomycin. However, drug-resistant *S. pneumoniae* has become increasingly prevalent. Age  $\geq 65$  years has been identified as a risk factor for  $\beta$ -lactam-resistant *S. pneumoniae*. Resistance to penicillin and cephalosporins

appears to be decreasing but macrolide resistance continues to increase. Repeated use of fluoroquinolones predicts an increased risk of infection with fluoroquinolone-resistant pneumococci (12). Because nursing home residents in particular have usually been exposed to multiple courses of antibiotic therapy, they have a higher risk for harboring drug-resistant pneumococci, gram negatives, and *S. aureus*. If empirical therapy with piperacillin-tazobactam and vancomycin results in treatment failure, vigorous attempts should be made to identify a causative pathogen and broadening antibiotic coverage to a carbapenem may be warranted. For those nursing home residents that are not transferred to a hospital facility and are empirically treated for NHAP at the nursing home, intramuscular once-daily cefepime has been shown to have clinical success and be more cost-effective than ceftriaxone. Of 61 participants (32 received cefepime, 29 received ceftriaxone) that could be evaluated, clinical success occurred in 78% of cefepime- and 66% of ceftriaxone-treated patients ( $P = 0.39$ ). Mean antibiotic costs were  $\$117 \pm 40$  for cefepime- and  $\$215 \pm 68$  for ceftriaxone-treated patients ( $P < 0.001$ ) (25). For those residents in whom empirical ceftriaxone therapy would be used, intramuscular cefepime at the nursing home can be considered. If treatment in the nursing home setting is preferred with an oral antimicrobial agent, then ciprofloxacin can be administered to cover most of the causative pathogens.

### **Pathogen-Directed Therapy**

Once the etiology of pneumonia is identified, antimicrobial therapy should be directed at that pathogen. A list of preferred and alternative antimicrobial agents for the most common pathogens identified in older adults is provided in Table 2 (12). Since many older adults are colonized with more drug-resistant organisms, extended spectrum  $\beta$ -lactamase (ESBL)-producing organisms have been increasingly isolated. Ertapenem, a newer carbapenem with narrower spectrum of activity than meropenem or imipenem, has been shown to have clinical utility in VAP in older adults (26).

### ***Prevention***

The mainstay for the prevention of pneumonia in older adults is pneumococcal and influenza vaccination. As per the Centers for Disease Control and Prevention guidelines, all persons age 65 or older should receive pneumococcal vaccine once. Revaccination is not recommended unless the first dose was administered under the age of 65 in which case revaccination should occur at age 65 if 5 years have passed since vaccination. Since 90% of all influenza-related deaths occur among people aged at least 65 years, yearly influenza vaccination has been recommended; however, the actual benefits of influenza vaccination in older adults are controversial. Even as vaccination coverage increased from 15 to 65%,

**Table 2** Recommended antimicrobial therapy for specific pathogens for pneumo=nia<sup>12</sup>

Organism	Preferred antimicrobial	Alternative antimicrobial
<i>Streptococcus pneumoniae</i>		
Penicillin nonresistant (MIC < 2 µg/mL)	Penicillin G, amoxicillin	Macrolide, cephalosporins, clindamycin, doxycycline, respiratory fluoroquinolone
Penicillin resistant (MIC ≥ 2 µg/mL)	Base on susceptibility → cefotaxime, ceftriaxone, fluoroquinolone	Vancomycin, linezolid, high-dose amoxicillin (3 g/day with penicillin MIC ≤ 4 µg/mL)
<i>Haemophilus influenzae</i>		
Non-β-lactamase producing	Amoxicillin	Fluoroquinolone, doxycycline, azithromycin, clarithromycin
β-lactamase producing	Second- or third-generation cephalosporin, amoxicillin-clavulanate	Fluoroquinolone, doxycycline, azithromycin, clarithromycin
Mycoplasma pneumoniae or Chlamydophila pneumoniae	Macrolide, a tetracycline	Fluoroquinolone
<i>Legionella</i> species	Fluoroquinolone, azithromycin	Doxycycline
Enterobacteriaceae	Third-generation cephalosporin, carbapenem (drug of choice if extended-spectrum β-lactamase producer)	β-lactam/β-lactamase inhibitor, fluoroquinolone
<i>Pseudomonas aeruginosa</i>	Antipseudomonal β-lactam plus ciprofloxacin or levofloxacin or aminoglycoside	Aminoglycoside plus ciprofloxacin or levofloxacin
<i>Acinetobacter</i> species	Carbapenem	Cephalosporin-aminoglycoside, ampicillin-sulbactam, colistin
<i>Staphylococcus aureus</i>		
Methicillin susceptible	Antistaphylococcal penicillin	Cefazolin, clindamycin
Methicillin resistant	Vancomycin or linezolid	TMP-SMX, clindamycin, doxycycline
Anaerobe (aspiration)	β-lactam/β-lactamase inhibitor, clindamycin	Carbapenem
Influenza virus	Oseltamivir or zanamivir	
<i>Mycobacterium tuberculosis</i>	Isontiazid plus rifampin plus ethambutol plus pyrazinamide	

<sup>12</sup>Reference 12

recent excess mortality studies did not demonstrate a decline in influenza-related mortality since 1980 (27). Impaired antibody responses are thought to contribute to stable mortality rates. Booster influenza vaccines have been shown to augment antibody responses among nursing home residents with an impaired response to initial vaccination; however, improved seroprotection rates were not shown to decrease hospitalization rates, death, or antibiotic use in a year without circulating influenza (28). One possible explanation for poor responsiveness to influenza vaccine is age-related impairment in innate immunity, specifically Toll-like receptor (TLR)-mediated expression of the B7 costimulatory molecules CD80 and CD86 which are critical for vaccine immunity (29). Therefore, only yearly influenza vaccination is currently recommended, but future attempts at improved vaccine strategies are warranted.

Since inadequate oral care and swallowing difficulty have been identified as independent modifiable risk factors for NHAP, interventions targeted towards improving oral hygiene and swallowing (e.g., mechanical oral care, 0.12% oral chlorhexidine rinsing) need to be tested to determine whether they can reduce the incidence of pneumonia. In a recent pilot evaluation in two nursing homes, it was demonstrated that mechanical oral care (i.e., teeth and/or denture and oral cavity brushing) plus 0.12% oral chlorhexidine rinses were feasible to perform by certified nurses aides, were adhered to by nursing staff, and were effective in improving oral hygiene (i.e., reduction in oral plaque scores) and swallowing difficulty (Vincent Quagliarello, 2009). Additional interventions to improve swallowing need to be investigated as well. The traditional Chinese herbal medicine Banxia Houpu Tang (BHT) found to improve swallowing reflex in patients with stroke and Parkinson's disease has been tested in a randomized controlled trial among elderly nursing home residents and was found to reduce the risk of pneumonia and pneumonia-related mortality (30). Likely, a combination of interventions to improve oral hygiene and swallowing difficulty will have the greatest potential of reducing the burden of pneumonia in nursing home residents. Future studies will determine whether a similar strategy will reduce the burden of pneumonia in elderly community dwellers.

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# Tuberculosis in Older Adults

Chad R. Marion and Kevin P. High

## Key Points

- Despite comprising only 15% of the total population, older adults (age 65 years and over) account for the majority of active tuberculosis (TB) and residents of long-term care are at particularly high risk.
- Aging of the immune system (i.e., immune senescence), poor nutrition (particularly vitamin D deficiency), and comorbidities contribute to the risk of *Mycobacterium tuberculosis* reactivation in older adults.
- When compared with young adults, older adults are less likely to have classic symptoms of TB which include fever, night sweats, hemoptysis or weight loss, but they are more likely to present with nonspecific symptoms such as dizziness and mental “dullness.”
- Radiographic changes in older adults with pulmonary TB are less likely to be upper lobe and cavitary than in younger adults; further, pulmonary TB in older adults is often mistaken for community-acquired pneumonia, an error that can lead to delayed diagnosis/treatment, exposure of healthcare workers to TB, and an increased risk of drug resistance.
- Treatment of TB does not vary by age but toxicities of anti-tuberculous therapy may be more prevalent with advanced age, and drug interactions are common.

## Epidemiology and Clinical Relevance

Tuberculosis (TB), caused by the bacterium *Mycobacterium tuberculosis*, is a worldwide health problem. The World Health Organization (WHO) estimates that throughout the world one person is infected every second, resulting in approximately

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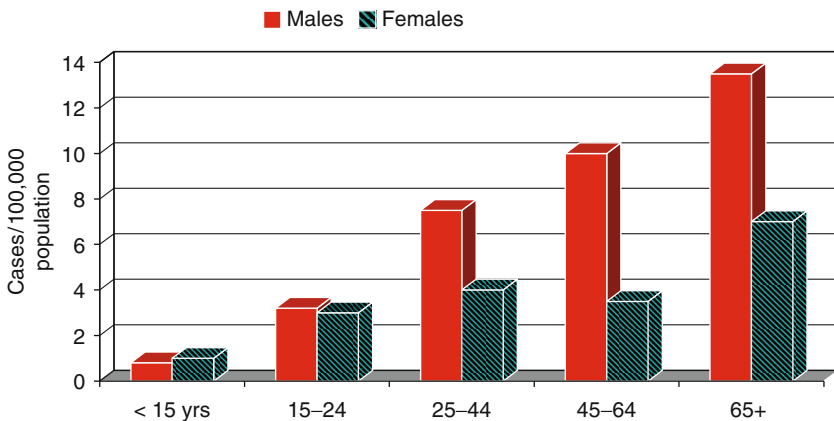
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one in every three persons currently infected. Additionally, the WHO estimates that of the 300 million who will be infected, 90 million will develop disease, and 30 million will die due to tuberculosis in the next decade. Despite these daunting figures, the incidence of TB is falling in many developed countries, but the trend is not uniform. For example, since the early 1990s, the Baltic States have experienced a steady increase in reported TB cases (1).

Older adults are uniquely susceptible hosts for TB. In the United States, the number of individuals age 65 and older is increasing rapidly, and this population represents a distinct cohort in relation to TB infections with a rate of 11.5 cases/100,000 population vs. 6.0 cases/100,000 in the general population. Chan and Welch reported that the United States elderly population, which makes up 13% of the population, accounts for 53% of the reported TB cases (2). A similar preponderance of older adults is seen in WHO data from developing countries (e.g., Mexico, 14.9/100,000 in those <65 years vs. 45.8/100,000 in those ≥65 years), and developed countries (e.g., Canada, 9.6/100,000 young adults vs. 28/100,000 in older adults) (2, 3). Interestingly, however, different sub-populations within a country may have varying TB epidemiology with regard to age. Van den Brande reported the expected gradual increase in the incidence of reported TB cases in Belgian natives over the age spectrum from about 5/100,000 in young adults in their 20s to about 25/100,000 in those 75 years and over. In contrast, adult immigrants in Belgium demonstrated much higher rates in all age groups (about fourfold higher than native Belgians), but a bimodal distribution was noted with very high rates (about 75/100,000) in young adults (20–30 years) and older adults (60–70 years), but lower rates in middle aged adults (40–50) of only 20–40/100,000 (4).

The aged population can be further subdivided into risk groups based on dwelling and gender. At every age beyond the third decade, men have a higher risk of clinical TB than women (5) (Fig. 1). Nursing home (NH) residents have up to a fourfold higher risk for clinical TB than community-dwelling elderly (234/100,000 in the NH



**Fig. 1** Incidence of active tuberculosis by age and gender; data from (5)

elderly vs. 60 cases/100,000 in the community); however, because only 5% of older adults live in nursing facilities, 80% of the reported cases of TB are in community-dwelling elderly. Females outnumber men in the NH by 2:1; however, male NH residents have a twofold to threefold higher risk of contracting TB than women. In the United States, TB infection prevalence in NH residents for men is 1,000 cases/100,000, while females have a prevalence of 376 cases/100,000 (2). Interestingly, upon admission to NH, only 5–10% of NH residents have purified protein derivative (PPD)-positive screening tests, but PPD reactivity has a prevalence of 21–50% in general screening of NH residents, suggesting transmission to residents after NH admission. The risk of clinical disease in PPD-positive patients is 2–3% per year, and the risk of TB in those with a recent PPD-positive conversion is 8% in women and 12% in men; this is the basis for yearly screening in high-risk groups (see section “Prevention” (2, 3)).

## ***Biologic Predisposition of Older Adults to Clinical Illness***

### **Pulmonary Changes in the Aged**

Anatomic structures in the lung and pulmonary functions change significantly with age (2). It is not well delineated whether these changes are due to the aging process itself, comorbid conditions, or a combination, but at least some change appears to be independent of comorbidity, as pulmonary function does decrease, even in the healthy elderly, and changes have been detected as early as age 40. The principal anatomic changes, which are thought to be secondary to changes in the connective tissue of lung parenchyma, lead to smaller airway sizes. Studies have shown that in healthy, non-smoking elderly, there is a progressive decrease in the forced expiratory volume in one second (FEV1) and the forced vital capacity (FVC) while total lung capacity (TLC) is maintained. The result is increased “dead space” despite a stable TLC. These changes are somewhat related to gender with FEV1 in men showing a decline beyond age 40 of 14–30 ml/year and in women a decline of 15–24 ml/year. It is believed that these changes may be related to the decreased chest wall compliance from kyphosis, scoliosis, and respiratory muscle weakness in the aged or co-existent conditions such as arthritis.

Additional changes in lung function are also common with age. Ventilation–perfusion mismatch is more common in the elderly population than in young adults, and several factors are thought to contribute to this mismatch. Examination of morphology in animal models shows an increase of the collagen to elastic tissue ratio in alveolar tissue with age. Further, there is a decrease in lung recoil and expiratory flow in the elderly. These changes are thought to contribute to the decline in diffusion capacity of the lung, perhaps increasing the probability that older adults will suffer greater compromise of gas exchange vs. young adults with a similar burden of disease.

## *Immunologic Changes in the Aging*

Nearly all TB in older adults represents reactivation of infection that was acquired much earlier in life, suggesting that reduced host defenses which previously contained the infection assume a major role in clinical disease. Anatomical, physiological, sociological, and economic factors as well as comorbidities all have a role in suboptimal functioning of the immune system in older adults. A meta-analysis of 12 studies of adults with TB demonstrated that older subjects had a higher incidence of cardiovascular disease, chronic obstructive pulmonary disease, diabetes mellitus, gastrectomy, and neoplasia (3).

The phenomenon of immune senescence and age-related decline of immune competence also impacts TB risk; the T-cell compartment is most affected by age and is essential for host defenses vs. mycobacteria. Thymic atrophy, reduced numbers of naïve T cells, declines in T-cell diversity, and a decrease in IL-2 and IL-2 receptor expression are well documented with advanced age. In addition, reduced expression of the co-stimulator molecule CD28 on CD8+ T cells occurs with advancing age, perhaps related to chronic activation in response to cytomegavirus or other chronic viruses, and is a marker of T-cell senescence. The T-cell senescent phenotype is correlated with shortened telomeres, marked expression of inflammatory cytokines and impaired vaccine responses (see also chapter “Factors Predisposing to Infection”); however, the relation of T-cell senescence markers has not been examined with specific regard to risk of tuberculosis.

Recent elucidation of immune mechanisms important in TB control suggests other pathways may be impaired in older adults. Due to decreased sun exposure and lack of intake of dairy products, vitamin D deficiency is common in older adults; studies in NH residents suggest vitamin D deficiency is present in 20–40% (see also chapter “Nutrition and Infection”). Vitamin D has recently been shown to be a critical link in host defense vs. TB through mechanisms tied to toll-like receptor activation (6). Waning of vitamin D-related mechanism of resistance may contribute further to the risk of clinical TB in older adults.

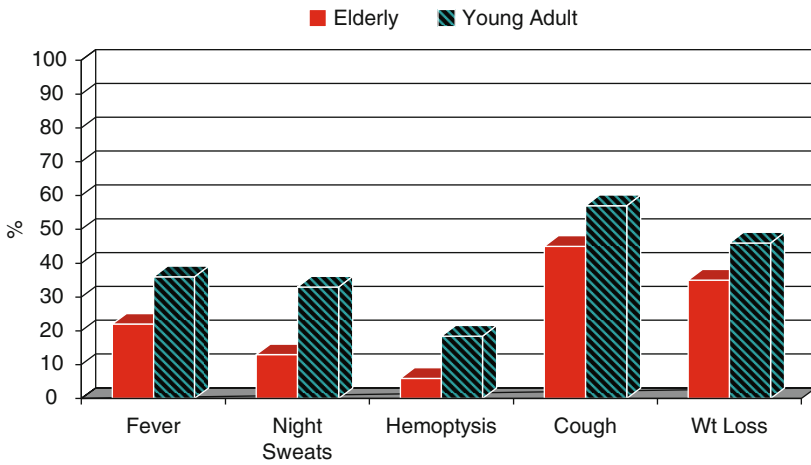
## **Risk Factors and Clinical Manifestations of TB**

The risk factors for clinical TB differ somewhat in older vs. young adults and were examined in a meta-analysis of subjects with pulmonary TB (3). Those studies demonstrated that alcoholism is more likely to be present in young adults, while older adults are more likely than young adults to have concomitant cardiovascular disease, diabetes mellitus, chronic obstructive pulmonary disease, cancer, or gastrectomy. In those with clinical disease, serum albumin levels and peripheral blood leukocyte counts are higher in young adults than older adults. These laboratory changes suggests that poor nutritional status is a major risk factor in older adults, but, at the time a patient presents for medical care, it is often difficult to distinguish pre-morbid malnutrition from disease-associated wasting.

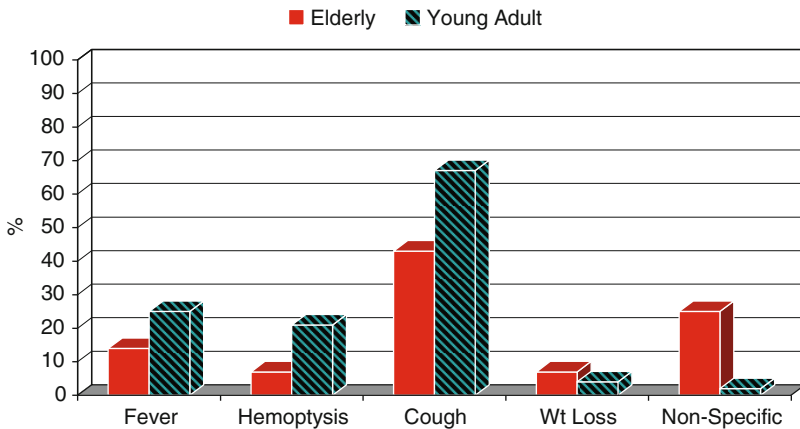
### Specific Descriptions of TB Clinical Illness

#### Pulmonary TB

Pulmonary TB is by far the most common form of TB in the elderly population (7, 8), and older adults with pulmonary TB may present with typical symptoms; however, young patients are more likely than older patients to experience classic symptoms of TB, including hemoptysis, night sweats, and fever (Figs. 2 and 3). Older patients are more likely to present with complaints of dyspnea, perhaps due



**Fig. 2** Symptoms in young (<65 years) and older (age 65 years and over) adults in Canada presenting with pulmonary and/or pleural tuberculosis (10) ( $p < 0.05$  for fever, night sweats and hemoptysis)



**Fig. 3** Presenting symptoms in young (<65 years) and older (age 65 years and older) adults in Hong Kong with pulmonary tuberculosis (9) ( $p < 0.05$  for hemoptysis and non-specific presentation)

to the increased dead space in the lung described above, and are more likely to have nonspecific complaints such as dizziness, abdominal pain, or “mental dullness.” The nonspecific presentation likely also reflects the fact that older adults with pulmonary TB more frequently present with miliary disease than young adults (3, 9, 10).

### **Miliary TB**

Miliary or disseminated TB often occurs in aging patients; many cases are very difficult to diagnose, and, without a high index of suspicion on the part of the healthcare provider, disease may only be identified in post-mortem examination. Clinical features include fever, weight loss, and hepatosplenomegaly often without other focal signs. Miliary TB should be considered in the differential diagnosis of “fever of unknown origin,” but failure to thrive (wasting, poor appetite, weakness) in the absence of fever is also a well-described presentation. The classical radiographic evidence of miliary mottling on the chest radiograph may not be present as well.

### **Tuberculous Meningitis**

In the elderly, tuberculosis meningitis occurs as a consequence of reactivation of a dormant focus or as a part of miliary infection. Unless masked by pre-existing cognitive impairment, older patients typically present in a fashion similar to their younger counterparts with a subacute onset of fever, headache, and confusion with simultaneous or preceding systemic symptoms of weakness, anorexia, and fatigue. Some older patients can also present with unexplained cognitive decline or obtundation without fever or nuchal rigidity; in such patients, it is imperative to maintain a high index of suspicion for tuberculosis meningitis until proven otherwise. One should strongly consider TB in any older adult with neurologic symptoms and cerebrospinal fluid findings of pleocytosis (typically lymphocyte predominant except in very early stages), a high protein and/or low glucose. Tuberculosis meningitis is associated with very high mortality in the elderly and neurological deficits are common in survivors.

### **Skeletal TB**

In the elderly, skeletal TB infection commonly affects the lumbar and thoracic spine, but cervical spine disease is rare. Paravertebral abscesses or “cold abscesses” are often associated with spinal infection. Primary symptoms of spinal TB consist of pain over the involved vertebrae; neurological deficits and sinus tracts may occur with more advanced disease. Low-grade fever, weight loss, fatigue, and anorexia may be, but are not universally, present. Tuberculosis arthritis more commonly involves the large weight-bearing joints; however, in the elderly, peripheral joints (e.g., knees,

wrists, ankles) may be involved. Because older patients often have degenerative joint disease, the diagnosis of coexisting tuberculosis arthritis may be overlooked.

## **Genitourinary TB**

Although genitourinary (GU) TB is seen in a significant number of elderly persons, this form of TB disease largely occurs in persons in their third, fourth, and fifth decades of life. The kidney is the major site of involvement with as many as 20–30% of patients being asymptomatic. Genitourinary TB can also involve the ureters, bladder, prostate, epididymis, and seminal vesicles. Presenting symptoms may include dysuria, frequency, flank pain, and hematuria. The diagnosis must be considered in the presence of abnormal urinary sediment, pyuria without bacteruria or hematuria. Significant disease may result in pelvic or scrotal masses and draining sinuses; systemic manifestations (fever, anorexia, weight loss) may be absent.

## **Diagnostic Tests**

### ***Tuberculin Skin Testing***

Purified protein derivative (PPD) has been used for tuberculin skin testing (TST) for decades assisting in the diagnosis of clinical illness and remaining the clinical standard of care for identifying patients with latent *M. tuberculosis*. Definitions for PPD positivity vary based on underlying illness, risk factors, and domiciliary setting (Table 1) (11). Most older adults have conditions that pose a moderate risk for contracting active TB (diabetes, chronic obstructive pulmonary disease, nursing home residence, etc) and thus an induration of  $\geq 10$  mm is a positive test. However, in conditions of high risk of active TB only  $\geq 5$  mm of induration is required for positive TST.

Older adults, most likely due to immune senescence and co-morbid illness, have a lower response rate to TST than young patients. In a Canadian study of adults with clinically apparent TB, only 63% of older adults (age 65 and over, mean 74 years) were PPD positive, while 86% of young adults (under age 65, mean 41 years) were PPD positive (10) (Fig. 4).

The diagnosis of latent TB is employed in screening programs in high-risk groups. For most older adults, this is pertinent in the long-term care setting. “Two-step” testing is recommended for initial testing followed by annually testing of all long-term care residents as outlined in section “Prevention.”

### ***Blood Interferon Testing***

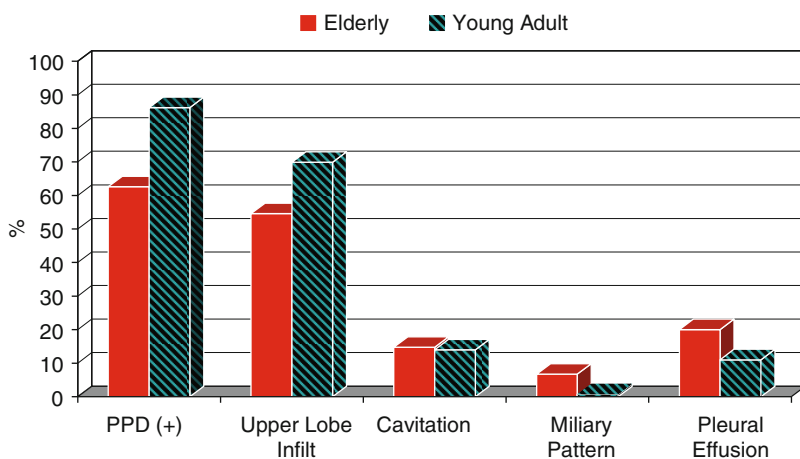
New blood tests to detect TB measure interferon (IFN)-gamma production by memory T-cells in response to mycobacterial antigens specific for *M. tuberculosis*.



**Table 1** Criteria for positive PPD in different risk conditions (from <http://www.cdc.gov/tb/pubs/tbfactsheets/skintesting.htm> – accessed May 24, 2008)

≥5 mm induration	≥10 mm induration	≥15 mm induration
HIV-infected persons	Recent immigrants (<5 years) from high-prevalence countries	Any person, including persons with no known risk factors for TB.
<b><i>A recent contact of a person with TB disease</i></b>	Injection drug users	However, targeted skin testing programs should only be conducted among high-risk groups
<b><i>Persons with fibrotic changes on chest radiograph consistent with prior TB</i></b>	<b><i>Residents and employees of high-risk congregate settings (includes long-term care facilities)</i></b>	
	Mycobacteriology laboratory personnel	
	Persons with clinical conditions that place them at high risk	
	Children <4 years of age	
	Infants, children, and adolescents exposed to adults in high-risk categories	
-Patients with organ transplants		
Persons who are immunosuppressed for other reasons (e.g., taking the equivalent of >15 mg/day of prednisone for 1 month or longer, taking TNF-α antagonists)		

Risk conditions common in older adults are highlighted by bold-italics. *TB* tuberculosis, *HIV* human immunodeficiency virus, *TNF-α* tumor necrosis factor alpha



**Fig. 4** Characteristics of tuberculin skin testing and radiography in young vs. older adults in Canada with active pulmonary and/or pleural tuberculosis (10) ( $p < 0.05$  for PPD (+) and miliary pattern). *PPD* purified protein derivative

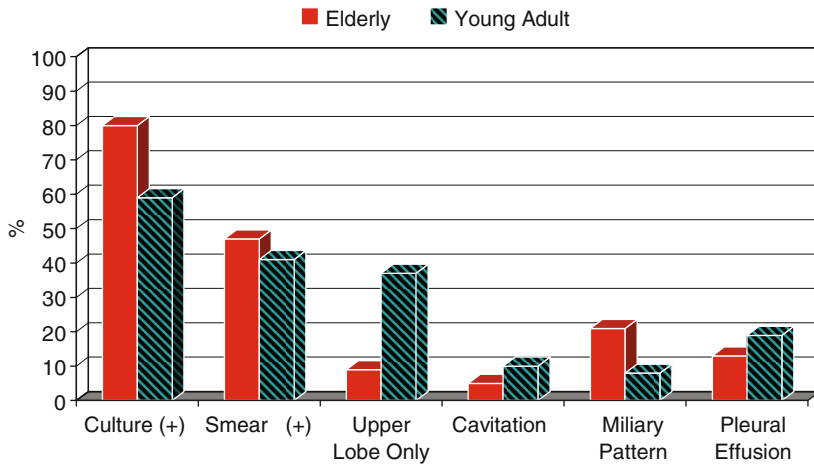
The sensitivity of the IFN-gamma tests are approximately 80% vs. 70% for TST in general studies of those with clinical illness; since the antigen used is not related to Bacillus Calmette-Guérin (BCG) and allows differentiation of a positive TST due to BCG vs. exposure to TB, the specificity of the test is most valuable in those with prior BCG immunization; however, these tests may not meet expectations of their initial promise and hope of increasing sensitivity for the diagnosis of TB in older adults. Mori et al. showed that, like TST, the sensitivity of IFN-gamma testing wanes with age (12); in fact, in older age groups, when examining an elderly population known to have a very high prevalence of exposure to *M. tuberculosis* early in life, TST was *more* sensitive than IFN-gamma detection.

### ***Smear/Cultures***

Microbiologic methods, smears, and cultures, for *M. tuberculosis* remain the gold standard for definitive diagnosis but are insensitive when compared with microbiologic specimens for routine bacteria. Histologic examination of tissue from various sites such as the liver, lymph nodes, bone marrow, pleura, or synovium that show the characteristic tissue reaction (caseous necrosis with granuloma formation) is useful for the diagnosis of TB disease, but does not definitively identify *M. tuberculosis* as the causative agent nor allow susceptibility testing of organisms; therefore, culture should be obtained whenever possible. For suspected pulmonary TB, three consecutive morning sputum specimens are recommended for mycobacterial studies that include an initial smear and culture for *M. tuberculosis*. Elderly persons unable to expectorate sputum should be considered for a more aggressive diagnostic intervention and flexible fiberoptic bronchoscopy is valuable for the microbiologic confirmation of TB.

Both the Ziehl–Neelson (heating) and Kinyoun (phenol) staining methods utilize carbolfuchsin and stain the organism red against a blue or green counter-stain. Auramine–rhodamine dye applies the fluorochrome method in which the mycobacterial cells appear golden-yellow against a dark background is more sensitive than classical staining methods. Importantly, all stains merely identify the presence of acid-fast organisms but they do not identify a species. Important acid-fast organisms that may be confused with TB include non-tuberculous mycobacteria, *Legionella* spp., and *Nocardia* spp.

Current mycobacterial culture methods are able to more rapidly grow and identify organisms than in the past utilizing radiometric systems, specific DNA probes, or polymerase chain reaction (PCR) (13). Most laboratories can identify the species of mycobacterium isolated within 24–48 h after sufficient growth is noted in liquid or on solid media; however, drug susceptibility testing still requires weeks of culture on classical media. Mycobacterial cultures may be more likely to be positive in older adults than in young adults, perhaps due to a greater organism burden, although studies examining rate of culture positivity lacked sufficient power to definitively determine a difference cultures (9) (Fig. 5).



**Fig. 5** Microbiologic and radiographic findings in young vs. older adults in Hong Kong with active pulmonary tuberculosis (9) ( $p < 0.05$  for upper lobe only and military pattern)

### ***Radiographic Findings***

Radiographic findings, like other diagnostic modalities, vary with age (3, 9, 10, 14). Cavitations are more common in young than older adults with pulmonary TB. Further, young patients have more upper lobe infiltration while older patients are more likely to have a miliary or nonspecific pattern on chest radiograph. Nonspecific radiographic changes occasionally lead to difficulty in differentiating community-acquired pneumonia (CAP) from pulmonary TB in older adults, particularly those who present with subacute symptoms. One multivariate analysis (3) found that symptoms over 2 weeks, weight loss, and lymphopenia were associated with TB infection in the elderly while the more stereotypical night sweats, upper lung involvement, cavitation on chest x-ray and white blood count  $<12 \times 10^3/\text{mm}^3$  could not differentiate TB from CAP. Misdiagnosing TB pulmonary infection as CAP can lead to delayed diagnosis of TB and to unnecessary exposures of healthcare workers and family members/visitors to *M. tuberculosis*. One study showed that 14.4% of patients with pulmonary TB were started on empirical fluoroquinolone (FQ) therapy for presumed CAP prior to the diagnosis of TB being considered. Empirical treatment with FQs led to an average 34-day delay in TB treatment probably due to the activity of FQs against *M. tuberculosis* and was associated with more frequent hypoalbuminemia and negative outcomes in the aged (15); further, as with any single agent used to treat TB, FQ monotherapy leads to rapid development of resistance to FQs.

### **Treatment**

Medical therapy of TB does not vary by age. For treatment of active disease, initial four-drug therapy is recommended but, if the organism is isolated and susceptibility testing results are available, can be tapered to two-drug specific combination therapy.

**Table 2** Preferred treatment regimens for susceptible strains of *Mycobacterium tuberculosis* (<http://www.cdc.gov/tb/pubs/tbfactsheets/treatmentHIVnegative.htm>; accessed May 24, 2008)

Preferred regimen	Alternative regimen	Alternative regimen
Initial phase Daily INH (300 mg), RIF (600 mg), PZA, (15–30 mg/kg up to 2 g), and EMB <sup>a</sup> (15–20 mg/kg up to 1 g) for 8 weeks	Initial phase Daily INH, RIF, PZA, and EMB <sup>a</sup> for 2 weeks, then twice-weekly for 6 weeks	Initial phase Thrice-weekly INH, RIF, PZA, and EMB <sup>a</sup> for 8 weeks
Continuation phase Daily INH (300 mg) and RIF (600 mg) for 18 weeks or Twice-weekly INH (900 mg) and RIF (600 mg) for 18 weeks	Continuation phase Twice-weekly INH and RIF for 18 weeks	Continuation phase Thrice-weekly INH and RIF for 18 weeks

INH isoniazid, RIF rifampin, PZA pyrazinamide, EMB ethambutol

<sup>a</sup>EMB can be discontinued if drug susceptibility studies demonstrate susceptibility to first-line drugs. Doses are provided for the preferred regimen; other dosing recommendations are available at <http://www.cdc.gov/mmwr/PDF/tr/tr5211.pdf>

Common regimens used appear in Table 2 and are based on isoniazid (INH), rifampin, pyrazinamide, and ethambutol in most cases; due to the potential of nephrotoxicity, streptomycin is rarely used in older adults. Direct observed therapy (DOT) by public health authorities is preferable in all cases of TB and has been associated with a lower risk of relapse and drug resistance; further, reporting of pulmonary TB to public health officials is mandatory and allows tracing of contacts for evaluation.

Multidrug resistant (MDR) TB is less likely in older adults than young adults (1–5) but does occur. The difference in drug resistance may be due to improved compliance in older adults and/or a lower prevalence of MDR TB when older adults were first exposed to the organism. A full discussion of the treatment of drug-resistant TB is beyond the scope of this chapter; however, if a patient is documented or highly suspected of having MDR TB or extensively drug resistant (XDR) TB, one should consult a specialist in the field and/or the CDC (<http://www.cdc.gov/tb/>) for the latest recommendations.

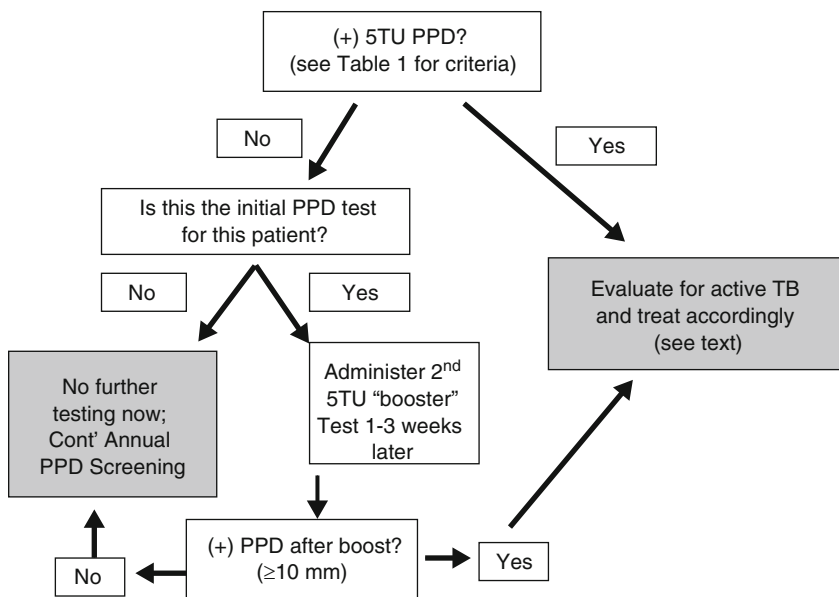
Adverse reactions of anti-tuberculous therapy are common and may be increased in the elderly, but there is no definitive data to confirm this common clinical suspicion. Common adverse reaction to INH, rifampin and pyrazinamide include asymptomatic increase in liver enzymes, hepatitis, and hepatotoxicity. Ethambutol adverse reactions include: rash and decreased red color discrimination and visual acuity. Streptomycin side effects include renal toxicity and cochlear-vestibular toxicity.

Drug–drug interactions are common with anti-TB therapy. INH increases the concentration of phenytoin, carbamazepine, warfarin, and diazepam. When administering prednisone, one needs to increase the dosing of INH. Rifampin decreases the concentration of methadone, digoxin, cyclosporine, warfarin, oral hypoglycemics, corticosteroids, theophylline, dapsone, phenytoin, and ketoconazole. Pyrazinamide interactions are limited to probenecid, which increases the concentration of pyrazinamide. Aluminum salts commonly present in antacids decrease absorption of ethambutol.

## Prevention

In United States, it is recommended that all nursing homes employ TST to identify older adults at risk for clinical disease (16, 17). The sensitivity of such testing is enhanced by initial two-step testing, where a second TST is placed 1–3 weeks after the first TST if the initial PPD is negative. After initial testing, all NH residents should receive annual TST screening. This algorithm is employed as part of the recommended diagnostic and treatment guideline for NH residents (Fig. 6).

Unlike clinically active TB, latent infection (identified typically by a (+) PPD in the absence of clinical symptoms or radiographic evidence of disease) can be treated with a single agent and should be considered in all patients who have not received prior treatment regardless of age (18) (also see July, 2007 update at <http://www.cdc.gov/tb/pubs/tbfactsheets/treatmentLTBI.htm>). For those with latent TB, 9 months of daily INH therapy or higher doses twice weekly remains the preferred drug regimen; alternatively, 4 months of rifampin daily may be given if INH is not tolerated or if the organism is known to be INH resistant. For recent TST converters, efficacy of INH reaches 98.5%; for those with long standing PPD positivity the efficacy for disease prevention is 85%.



**Fig. 6** Algorithm for tuberculin skin testing in residents of long-term care facilities incorporating two-step PPD testing in the initial screen. *Gray-filled boxes* represent decision points for further evaluation or continued screening. *PPD* purified protein derivative

## Summary

Most cases of TB occur in older adults due to reactivation of latent bacteria associated with waning immunity and comorbidity. The manifestations of TB in the aged are frequently more subtle than in young adults. Early recognition of the disease is essential for optimal treatment and public health measures. Aggressive screening strategies should be employed in high risk populations such as NH residents, and, if not previously provided, prophylactic therapy should be administered to all those with latent infection regardless of their age. Treatment of active disease is not different in older vs. young adults.

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<http://www.cdc.gov/tb/>.

# Infective Endocarditis

Vinod K. Dhawan

## Key Points

- Age is an important risk factor for infective endocarditis (IE) with the incidence ratio of those age 65 and older vs. those less than 65 being approximately 9:1.
- Approximately 80% of IE cases in the elderly are caused by *Staphylococcus aureus*, *Streptococcus* spp., and enterococci.
- Clinical manifestations of IE in older adults may be nonspecific, atypical, and resemble aging changes or other common age-related disorders.
- The major diagnostic tests of IE are three sets of blood cultures and echocardiography (transthoracic or transesophageal).
- Antibiotic therapy should be given with bactericidal drugs whenever possible and directed most often toward staphylococci, streptococci, and enterococci; duration of therapy will depend on valve site, presence of complications, organism, available antibiotics against the pathogen(s), and clinical and microbiological response.

## Epidemiology and Clinical Relevance

Infective endocarditis (IE) is a microbial infection of the endocardial surface. Despite improvements in diagnostic accuracy, medical therapy and surgical techniques, mortality of patients with IE remains high. Infective endocarditis is caused by a variety of bacteria, fungi, rickettsiae, and other agents. Because the vast majority of IE cases are caused by bacteria, the discussion will focus primarily on bacterial endocarditis. The overall incidence of IE ranges between 2 and 6 per 100,000 persons per year. The reported incidence of IE in the United States

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is ~1 per 1,000 hospital admissions (1). Despite improvements in health care, the incidence of IE has not decreased over the past decades; this apparent paradox is explained by a progressive evolution in risk factors for IE. While the classic predisposing conditions such as rheumatic heart disease have been all but eradicated, new risk factors for IE have emerged (2). The new risk factors include an increasing proportion of prosthetic valve placements and nosocomially-acquired disease and recognition that elderly individuals with degenerative valvular disease are the most vulnerable population (3, 4). Age has been shown as an important risk factor for IE, with an incidence rate ratio of 8.8:1 for age 65 years or older vs. age less than 65 years (5, 6). Several factors account for the increased incidence of IE in elderly patients (a) decreased pool of patients with rheumatic heart disease which predominantly affects the younger patients and predisposes to IE, (b) increased longevity of patients with underlying heart diseases through surgical interventions has expanded the pool of at-risk patients with older individuals, (c) the incidence of calcific/degenerative heart disease (typically seen in old age) and its related IE has increased commensurate with increased life expectation, (d) newer invasive therapeutic interventions, particularly intravenous catheters, pacemakers, and the dialysis shunts, to which the elderly are more likely to be subjected, have all increased the risk of bacteremia and subsequent IE among the elderly, and (e) more frequent prosthetic cardiac valve placement in recent years has added a unique category of patients at risk for IE, a larger proportion of which are elderly.

Degenerative valvular heart disease is becoming increasingly associated with endocarditis among the elderly; in Israel, it was noted to be the most common underlying factor in patients with native valve endocarditis (5). Degenerative valve lesions have been found in 50% of patients over age 60 years with IE (7). Common lesions include degenerative aortic valve disease (occurring on a previously normal valve or complicating a bicuspid aortic valve), calcified mitral annulus, and calcific aortic stenosis. In degenerative calcification, the normal aortic valve occurs with advancing age and causes functional stenosis due to the restricted mobility of its cusps. The resulting turbulence predisposes the elderly patient to IE. Autopsy findings have revealed calcification of congenitally bicuspid valve to be the most frequent cause of aortic stenosis between 60 and 75 years (8). Likewise, progressive calcification of mitral annulus occurs with advancing age, taking place in 3.2% of women before the age of 70, but increases to 44% of females above the age of 90 (9). Patients with mitral valve prolapse and mitral regurgitation are more susceptible to IE, a risk particularly more pronounced in men older than 45. It has been noted that 42% of nursing home patients above age 60 have one or another underlying cardiac abnormality predisposing them to IE (10).

Infective endocarditis in older patients is somewhat more common in the males. Male to female ratio is 2–8:1 in patients older than 60 years of age (6, 11). In elderly people with IE, mitral valve involvement is more frequent. In a series of 44 elderly patients with endocarditis diagnosed by the Duke criteria, mitral valve was affected in 20 (45%), aortic valve in 14 (32%), and both the mitral and aortic valves were involved in 2 (5%) patients (12). Similarly, a retrospective review of endocarditis (diagnosed by the Duke criteria) noted mitral valve involvement in 52% of the

elderly whereas the aortic valve was the site of involvement in 55% of younger patients (13).

The development of IE is the net result of the complex interaction between the bloodstream pathogen with matrix molecules and platelets at sites of endocardial cell damage. The following sequence of events is thought to result in IE: formation of nonbacterial thrombotic endocarditis (NBTE) on the surface of a cardiac valve or damaged endothelial surface, bacteremia, adherence of the bacteria in the bloodstream to NBTE, and proliferation of bacteria within the vegetation. Infective endocarditis can occur from virtually any source of bacteremia, fungemia, or spread of other organisms within the blood. Bacteremia originating from oral cavity is especially important as viridans streptococci are particularly well adapted to infect cardiac valves; this explains their predominance in patients with IE. Additionally, disruption of the integrity of the skin barrier permits invasion by *Staphylococcus aureus* and *Staphylococcus epidermidis*, increasing the risk of IE. It is possible for IE to complicate bacteremia originating from urinary tract or gastrointestinal tract with resident organisms, especially enterococci.

## Etiologic Pathogens

The predominant organisms responsible for ~80% cases of IE in the elderly are *S. aureus*, *Streptococcus* spp., and enterococci. Over the last decade a novel methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged, which is primarily associated with healthy individuals within the community. In terms of epidemiology, microbiology, and clinical manifestations, this organism is distinct from healthcare-associated MRSA. The incidence of IE due to MRSA is increasing, and it carries a worse prognosis than IE due to methicillin-susceptible *Staphylococcus aureus* (14, 15). Some studies have noted a higher prevalence of enterococci among the elderly with IE (16). Also, *Streptococcus bovis*, an organism associated with colonic malignancy, may be noted more commonly in the elderly with IE. HACEK group of organisms (*Haemophilus* spp., *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*) may be occasionally responsible. *Staphylococcus lugdunensis*, a relatively virulent coagulase-negative staphylococcal species, may cause IE in older patients (17); it causes a rather acute disease with rapid valve destruction and paravalvular leak. Nosocomial endocarditis has emerged as a significant entity. In a recent study, it accounted for 22% of 109 cases overall and 16% of cases excluding early prosthetic valve endocarditis in cardiac surgery patients (18). Nosocomial endocarditis is important because of its case fatality rate of greater than 50%. Intravascular and urinary catheters in the elderly may trigger bacteremia and IE. Staphylococci and enterococci are the most common organisms in nosocomial IE. In one report, up to 13% of nosocomial *S. aureus* bacteremia resulted in IE (19). Newly identified pathogens, which are difficult to cultivate (e.g., *Bartonella* spp and *Tropheryma whipplei*) are present in selected individuals.

## Clinical Manifestations

In the elderly, the diagnosis and treatment of IE is particularly challenging and requires sound clinical judgment, a high index of suspicion, and careful monitoring for complications (20–22). The presentations of IE in the elderly are often nonspecific and atypical, resulting in delayed diagnosis (23–25). The febrile response is often blunted in older patients. Older patients with IE frequently present with constitutional symptoms such as lethargy, fatigue, malaise, anorexia, backache, arthralgia, and weight loss, all of which may be attributed to aging and other disorders more likely among the elderly. Some elderly patients manifest worsening of their congestive heart failure. Infective endocarditis may be complicated by paravalvular abscess formation, and embolic events, the most worrisome of which is a stroke. In addition, septic arthritis, vertebral osteomyelitis, pericarditis, metastatic abscesses, peripheral nervous system abnormalities, and a variety of renal complications ranging from immune-complex glomerulonephritis to renal abscesses may be noted. New cardiac murmurs, due to progressive valvular damage and valvular incompetence, are highly indicative of IE. However, about a third of patients with tricuspid valve disease, and those with only mural involvement, may not have a pathologic murmur on initial presentation. Additionally, heart murmurs in the elderly may be erroneously attributed to the underlying valvular calcification and, therefore, neglected. In 1994, Durack et al., refined the existing clinical criteria for the diagnosis of IE through incorporation of echocardiographic findings (26). The accuracy of clinical diagnosis of IE has greatly improved with the Duke criteria (see Table 1) (27). Studies, using the Duke criteria for the diagnosis of IE, have found no relevant differences in the frequency of fever, heart failure, embolic events, neurological symptoms, distribution of causative organisms, and cerebral deficit at the time of discharge of older patients as compared to that of their younger counterparts (12, 13). To the contrary, renal insufficiency on admission and malignancy are significantly more common among elderly patients with IE (12, 13).

**Table 1** Modified duke criteria for diagnosis of infective endocarditis

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Major criteria

1. Blood cultures positive for infective endocarditis (IE)
    - (a) Typical microorganism consistent with IE from two separate blood cultures as noted below
      - (i) Viridans streptococci, *S. bovis*, *S. aureus* or HACEK group or
      - (ii) Community-acquired enterococci in the absence of a primary focus; or
    - (b) Microorganisms consistent with IE from persistently positive blood cultures defined as
      - (i) At least 2 positive cultures of blood samples drawn >12 h apart, or
      - (ii) All of 3 or a majority of 4 or more separate cultures of blood, the first and the last sample drawn >1 h apart; or
    - (c) Single positive blood culture for *Coxiella burnetii* or antiphase I IgG antibody titer >1:800
- 

(continued)

**Table 1** (continued)

## Major criteria

## Evidence of endocardial involvement

- (a) Positive echocardiogram for IE (TEE recommended for prosthetic valve, possible IE by clinical criteria, or complicated IE, i.e., paravalvular abscess) defined as
  - (i) 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 or
  - (ii) Abscess or
  - (iii) New partial dehiscence of valvular prosthesis or
- (b) New valvular regurgitation (worsening or changing or preexisting murmur not sufficient)

## Minor criteria

1. Predisposing heart disease or intravenous drug use
2. Fever  $\geq 38^{\circ}\text{C}$  ( $\geq 100.4^{\circ}\text{F}$ )
3. Vascular phenomenon: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial or conjunctival hemorrhage, Janeway's lesions
4. Immunologic phenomenon: glomerulonephritis, Osler's nodes, Roth's spots, rheumatoid factor
5. Microbiologic evidence: positive blood culture that does not meet a major criterion as noted above or serologic evidence of active infection with organism consistent with IE

## Diagnosis

## Definite endocarditis

1. Histologic/microbiologic evidence of infection at surgery or autopsy; or
2. Two major criteria or
3. One major and three minor criteria or
4. Five minor criteria

## Possible endocarditis

1. One major and one minor criterion or
2. Three minor criteria

## No endocarditis

1. Negative findings at surgery/autopsy, after antibiotic therapy for  $\leq 4$  days or
2. Firm alternative diagnosis or
3. Resolution of illness with antibiotic therapy for  $\leq 4$  days or
4. Failure to meet criteria for possible endocarditis, as above

Adapted from (26, 27)

HACEK = *Haemophilus* spp., *Actinobacillus actinomycetemcomitans*, *cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingae*

TEE = transesophageal echocardiogram; IgG = immunoglobulin G

## Diagnostic Tests

The clinical diagnosis of IE can be substantiated through laboratory examination and echocardiographic data. Leukocytosis with left shift is common, although leukopenia and thrombocytopenia are also noted rarely. Anemia may be present in the subacute disease. The erythrocyte sedimentation rate is elevated except in elderly patients with congestive heart failure. Microscopic hematuria, proteinuria, red blood cell casts, and bacteriuria may be noted on urine microscopy. Rheumatoid factor may be present, complement levels may decrease, and immune complexes may be noted.

The intravascular location of infection in IE is responsible for continuous and rather high-grade bacteremia. By obtaining three sets of blood cultures that are preferably

drawn from different sites at different time intervals (e.g., at least 15 min apart), the causative organism of IE can be recovered in about 98% of patients. Prior antibiotic therapy may lower this yield. Identification of the pathogen in culture-negative IE depends on special procedures, which comprise inactivating antibiotics in the culture media, prolonging incubation (>2 weeks), and serology. More recently, molecular approach of polymerase chain reaction amplification of specific gene targets and universal loci for bacteria (16S rRNA) and fungi (18S, 28S and 5.8S rRNA) and subsequent sequencing has been used to identify the etiologic agent in blood culture and heart valve material from patients with suspected IE (28–30). This approach is particularly helpful in patients with culture negative IE. However, microbial contamination of clinical samples may lead to false positive results.

Echocardiography has emerged as a major tool for the diagnosis and management of this disease (31). Transesophageal echocardiography (TEE) is more sensitive and specific than the transthoracic echocardiogram (TTE). Elderly patients are more likely to have predisposing valvular conditions, (e.g., degenerative and calcific lesions and prosthetic valves, which may decrease the sensitivity of TTE in detecting IE (16)). Its sensitivity is also decreased among elderly patients in the presence of obesity, chest wall deformities, and chronic obstructive pulmonary disease (32). However, TEE has overall increased the diagnostic yield of IE in the elderly patients by 45% (16). TEE, with its overall sensitivity of 90%, is also superior to TTE in detecting smaller (5 mm) vegetations, diagnosing valvular perforation, demonstrating valvular regurgitation, and in delineating aneurysm and periannular abscess formation.

Chest X-rays of patients with right-sided IE may reveal multiple round densities, cavitory multilobar infiltrates, and pleural effusions due to septic emboli. An electrocardiogram may show conduction defects secondary to interventricular septal abscess formation. Computerized tomographic scanning and magnetic resonance imaging of the head of patients manifesting central nervous system abnormalities may reveal macroscopic abscess in 0.5% and diffuse cerebritis in 0.9–3.8% due to IE with highly virulent organisms (33). Arteriography is useful in outlining the mycotic aneurysms.

## **Antibiotic Treatment**

Rational antibiotic therapy of IE requires identification of the microbial etiology. Empirical intravenous antibiotic therapy should be initiated promptly after blood and other appropriate samples have been taken for culture (34). Bactericidal antibiotics are a cornerstone of therapy. High concentrations of antibiotic in the serum are desirable to ensure diffusion into the vegetations. Long-term treatment is mandatory to kill dormant bacteria clustered in the infected foci. In the usual patient with a subacute presentation, therapy of IE should be directed at streptococci with a combination of penicillin with an aminoglycoside, (e.g., gentamicin). In the presence of an acute onset, where methicillin-susceptible staphylococci are considered more likely, therapy should be initiated with a semisynthetic penicillin such as nafcillin (or

vancomycin, in the presence of penicillin allergy or suspected methicillin resistance) along with an aminoglycoside, (e.g., gentamicin). Antibiotic therapy should be optimized upon identification of the causative organism. Therapeutic regimens recommended for the most commonly encountered pathogens in the elderly with IE are presented in Table 2.

Many experts use a 2-week regimen of penicillin along with gentamicin for penicillin-susceptible viridans streptococcal IE, but this regimen is frequently avoided in the elderly with fragile renal function. A randomized, multicenter, open-label study reported a 2-week regimen of 2 g ceftriaxone in combination with 3 mg/kg of gentamicin given once daily to be as effective as 2 g of ceftriaxone administered once daily for 4 weeks (35). The combination therapy group included 25 patients with ages ranging from 27 to 92 years (mean  $\pm$  SD, 59.5  $\pm$  15.5 years). Adverse effects were minimal in both groups. The data from the national registry of Sweden suggested that a shortened aminoglycoside treatment of enterococcal endocarditis, (i.e., for 2–3 weeks may be equally effective and potentially less nephrotoxic in the elderly) (36).

Uncomplicated right-sided IE, with a susceptible strain of *S. aureus* can usually be cured with a 2-week combination of semisynthetic penicillin (e.g., nafcillin) and an aminoglycoside (37). However, this abbreviated treatment has not been studied in the elderly patients and should be avoided due to the potential of aminoglycoside toxicity. Vancomycin is less rapidly bactericidal than nafcillin in vitro against *S. aureus*, especially at high inocula, resulting in clinical failure rates of ~40% (38). Vancomycin therapy should be reserved for staphylococcal endocarditis in the presence of methicillin resistance or severe penicillin allergy. There is no conclusive evidence that addition of rifampin to the standard antibiotic treatment for native valve endocarditis is useful (39). It carries the potential for hepatotoxicity, drug-drug interactions, and the emergence of resistant isolates (40). The role of newer antimicrobial agents such as quinupristin-dalfopristin and linezolid, in the treatment of IE due to antibiotic-resistant gram-positive cocci in the elderly has not been established (41). Failure of linezolid therapy was reported in two elderly patients who had endocarditis due to MRSA (42). Daptomycin therapy has been found to be effective in right-sided endocarditis (43).

Disease caused by *Brucella* spp responds to 3 months or more of treatment with the following: doxycycline (100–200 mg every 12 h) plus co-trimoxazole (960 mg every 12 h) or rifampin (300–600 mg daily) combined or not with streptomycin (16 mg/kg per day). Surgery might be needed for cure as defined by an antibody titer returning to less than 1:160. Disease associated with *Coxiella burnetii* is often treated for 3 years with doxycycline combined with a fluoroquinolone; however, recurrences are common. When the antigen against phase I IgG titer is less than 1:800 and IgM and IgA titers are less than 1:50, then treatment is considered successful. Infective endocarditis caused by *Bartonella* spp. responds to  $\beta$ -lactams (amoxicillin or ceftriaxone) combined with aminoglycosides (e.g., gentamicin) for at least 2 weeks or  $\beta$ -lactams combined with other drugs (e.g., doxycycline for 6 weeks or more). In at least 90% of cases, the combination of surgery with medical therapy is reported.

In order to optimize the doses of antibiotics, the impact of aging on specific drug kinetics should be considered. Due to impaired renal clearance in the elderly, doses

**Table 2** Treatment of elderly with infective endocarditis due to common pathogens

Pathogen	Antibiotic regimen
<b>Native valve endocarditis</b>	
Penicillin-susceptible streptococcus (MIC ≤ 0.1 µg/ml) <i>viridans</i> streptococci and <i>Streptococcus bovis</i>	Aqueous penicillin G, 2–3 mU IV q4 h × 4 weeks Aqueous penicillin G, 2–3 mU IV q4 h with gentamicin 3 mg/kg IV as a single daily dose or divided into equal doses q8 h × 2 weeks Ceftriaxone 2 g IV qd × 4 weeks Ceftriaxone 2 g IV qd with gentamicin 3 mg/kg IV as a single daily dose or divided into equal doses q8h × 2 weeks Vancomycin 15 mg/kg IV q12–24 h × 4 weeks
Relatively penicillin-resistant streptococcus (MIC >0.1 µg/ml and <0.5 µg/ml)	Aqueous penicillin G, 4 mU IV q4 h × 4 weeks with gentamicin 3 mg/kg IV as a single daily dose or divided into equal doses q8 h × 2 weeks Ceftriaxone 2 g IV qd × 4 weeks with gentamicin 3 mg/kg IV as a single daily dose or divided into equal doses q8h × 2 weeks Vancomycin 15 mg/kg IV q12–24 h × 4 weeks
Moderately penicillin-resistant streptococcus (MIC >0.5 µg/ml and <8.0 µg/ml) and nutritionally variant streptococci	Aqueous penicillin G, 4–5 mU IV q4 h with gentamicin 3 mg/kg IV as a single daily dose or divided into equal doses q8 h × 6 weeks Ceftriaxone 2 g IV qd with gentamicin 3 mg/kg IV as a single daily dose or divided into equal doses q8 h × 6 weeks Vancomycin 15 mg/kg IV q12–24 h × 4 weeks
Enterococci	Aqueous penicillin G, 4–5 mU IV q4 h with gentamicin 1 mg/kg IV q8 h × 4–6 weeks Ampicillin 2 g IV q4 h with gentamicin 1 mg/kg IV q8 h × 4–6 weeks Vancomycin 15 mg/kg IV q12–24 h with gentamicin 1 mg/kg IV q8 h × 4–6 weeks Ceftriaxone 2 g IV qd × 4 weeks
HACEK group organisms	Ampicillin/sulbactam 3 g IV q6 × 4 weeks Oxacillin, or nafcillin 2 g IV q4 h × 4–6 weeks with (optional) gentamicin 1 mg/kg IV q8 h for 3–5 days Cefazolin 2 g IV q8 h × 4–6 weeks with (optional) gentamicin 1 mg/kg IV q8 h for 3–5 days Vancomycin 15 mg/kg IV q12–24 h × 4–6 weeks Vancomycin 15 mg/kg IV q12–24 h × 4–6 weeks
Methicillin-susceptible staphylococci	Oxacillin, or nafcillin 2 g IV q4 h × 4–6 weeks with gentamicin 1 mg/kg IV q8 h for first 2 weeks with rifampin 300 mg q8 h PO × 6–8 weeks
Methicillin-resistant staphylococci <b>Prosthetic valve endocarditis</b>	Vancomycin 15 mg/kg IV q12–24 h × 4–6 weeks with gentamicin 1 mg/kg IV q8 h for first 2 weeks with rifampin 300 mg q8 h PO × 6–8 weeks
Methicillin-resistant staphylococci	

IV intravenous, *mu* million units, MIC minimum inhibitory concentration, *qd* once daily, HACEK *Haemophilus* spp., *Actinomyces actinomycetemcomitans*, *cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingae*, PO oral

of antibiotics including vancomycin, aminoglycosides and  $\beta$ -lactams should be adjusted appropriately. Most elderly patients achieve therapeutic levels with vancomycin dose administered once a day. For optimal dosing, serum concentration of vancomycin should be obtained. Elderly patients are particularly prone to the nephrotoxicity and the ototoxicity of aminoglycosides. Careful attention to renal function and aminoglycoside serum concentration are particularly important in older patients to minimize toxicity. When synergy with another agent is demonstrated, serum level of aminoglycoside lower than generally considered “therapeutic” may be adequate. Dose adjustment is also necessary for many  $\beta$ -lactams excreted predominantly by the kidneys; furthermore, many elderly patients are taking other medications for a variety of acute or chronic underlying diseases. As a consequence, it is important to consider potential drug interactions of these medications with antibiotics prescribed for IE.

In most patients, effective antibiotic therapy of IE results in defervescence of fever within a week. Those with persistent fever should be evaluated for the presence of a septic embolic focus (kidney, spleen, or liver), inadequate therapy, drug hypersensitivity, immune complex tissue injury, and valve ring abscess. Antibiotic therapy decreases the risk of first and recurrent embolization. With effective therapy the risk of embolization decreases from 17 events per 100 patient days in the first week to <5 events per 100 patient days during the second and third week (44). In general, elderly patients with IE generally have longer hospitalization as compared with the younger patients (42 days vs. 32 days in one study) (12).

## Role of Surgery

Several studies suggest that combined medical and surgical therapy of IE reduces mortality among patients with congestive heart failure, with perivalvular invasive disease, or with uncontrolled infection, despite appropriate antimicrobial therapy (45–47). Due to the improved surgical techniques and the availability of longer lasting prosthetic valves, patients with IE have been operated upon with acceptable morbidity and mortality. Results of studies on surgery for active IE indicate mortality rates of 8–16%, with actuarial survival at 5 years of 75–76% and at 10 years of 61% (48). Accepted indications for surgery in the setting of IE are summarized in Table 3 (49). While valve replacement is necessary for the left-sided IE, tricuspid valvectomy, or “vegetectomy” with valvuloplasty may be adequate for tricuspid valve disease. Elderly patients are at greater risk of postoperative complications (i.e., prosthetic dysfunction, pericardial tamponade, renal insufficiency, rhythm disturbances, and the necessity for a second intervention) (13). Video-assisted cardioscopy avoids the need for extended cardiac incisions and has been recently used successfully for resection of endocardial vegetations (50). Cardiac device-related (e.g., pacemaker) IE requires prompt hardware removal and prolonged parenteral antibiotic administration to decrease mortality among patients (51).



**Table 3** Indications for surgery in patients with infective endocarditis

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Persistent sepsis caused by a surgically removable focus or a valvular ring or myocardial abscess
Moderate to severe left heart failure due to valve dysfunction
Endocarditis due to organisms for which curative antimicrobial therapy is not available, e.g., fungi, rickettsiae, <i>Brucella</i> , vancomycin-resistant enterococcus
Prosthetic valve endocarditis with unstable prosthesis, progressive paravalvular leak or persistent infection after 7–10 days of appropriate antibiotic therapy
Persistent life-threatening embolization

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## Prosthetic Valve Endocarditis

With the advent of improved surgical techniques, a growing number of elderly patients receive bioprosthetic valves which places them at risk for subsequent IE. Prosthetic valve endocarditis (PVE) is a catastrophic complication of cardiac valve replacement associated with high mortality rates (52). The incidence of PVE seems to be increasing, ranging from 0.1 to 2.3 per patient-year (53). Prosthetic valve endocarditis is usually classified as early PVE (that is, acquired perioperatively) and late PVE (resulting from infections unrelated to the valve operation). Early PVE has a much worse prognosis than late PVE. Differences in infective organisms and in the clinical setting explain the dismal prognosis in early PVE and the almost universal need for surgical treatment in this type of PVE. Transesophageal echocardiography is an extremely useful diagnostic tool in PVE because it allows early recognition of vegetations that could not be visualized by transthoracic echocardiography; it is also the best tool to investigate periprosthetic damage and prosthetic dysfunction.

Antibiotic therapy of PVE should be empirically begun with a combination of vancomycin, gentamicin, and rifampin (Table 2). In cases with aggressive organisms (mostly non-streptococcal) that fail to respond immediately to antibiotics and cases with large periprosthetic leaks or abscesses, surgical treatment should be considered on an urgent basis provided the judicious assessment the clinical condition of the patient (age, comorbidities) favors this therapeutic option. The decision to operate, and the operation itself, should not be delayed.

Patients in whom the diagnosis has been made very early in the course of the disease are candidates for conservative management; these patients include the following: patients with streptococcal disease or with prompt antibiotic response, patients with reassuring echocardiographic findings such small or absent vegetations, no periprosthetic damage, and no severe prosthetic dysfunction. In these cases considered for medical treatment, the clinical course should be carefully monitored and, if any complication arises, reconsideration for surgical intervention should be initiated; therefore, only in patients at both ends of the prognostic spectrum (those with specific findings of less severe disease and those too ill to undergo an operation) is medical treatment likely to be the best choice. Furthermore, even if cure is achieved by medical treatment, close follow-up is mandatory to exclude progressive prosthetic dysfunction.

## Prevention

The American Heart Association has recently updated its recommendations for prophylaxis of IE (54). Prophylaxis is not recommended based solely on an increased lifetime risk of acquisition of IE. Administration of antibiotics solely to prevent endocarditis is not recommended for patients who undergo a genitourinary or gastrointestinal tract procedure. Infective endocarditis prophylaxis for dental procedures is recommended only for patients with underlying cardiac conditions associated with the highest risk of adverse outcome from IE and are listed in Table 4. For patients with these underlying cardiac conditions, prophylaxis is reasonable for all dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa. For effective prophylaxis, it is necessary to administer an appropriate antibiotic prior to a bacteremic episode (55). The prophylactic regimens currently recommended by the American Heart Association for dental procedures are listed in Table 5.

**Table 4** Cardiac conditions associated with the highest risk of adverse outcome from infective endocarditis (IE)

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Prosthetic cardiac valve or prosthetic material used for cardiac valve repair
Previous IE
Congenital heart disease (CHD)
Unrepaired cyanotic CHD, including palliative shunts and conduits
Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure
Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)
Cardiac transplantation recipients who develop cardiac valvulopathy

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Adapted from (54)

**Table 5** Infective endocarditis prophylaxis for dental procedures

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Situation	Agent and regimen: Single dose 30–60 min before procedure
Able to take oral medication	Amoxicillin 2 g PO
Unable to take oral medication	Ampicillin 2 g IM or IV <i>or</i> Cefazolin 1 g IM or IV <i>or</i> Ceftriaxone 1 g IM or IV
Allergic to penicillin	Cephalexin 2 g PO <sup>a,b</sup> <i>or</i> Clindamycin 600 mg PO <i>or</i> Azithromycin or clarithromycin 500 mg PO
Allergic to penicillin and unable to take oral medication	Cefazolin or ceftriaxone 1 g IM or IV <sup>b</sup> <i>or</i> Clindamycin 600 mg IM or IV

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*IM* indicates intramuscular, *IV* intravenous, *PO* oral; Adapted from (54)

<sup>a</sup>Or other first- or second-generation oral cephalosporin in equivalent adult dosage

<sup>b</sup>Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillin

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# Intra-abdominal Infections

Meghann L. Kaiser and Samuel Eric Wilson

## Key Points

- Intra-abdominal infections are more common in the elderly and carry greater associated morbidity and mortality.
- Intra-abdominal infections in the elderly have atypical presentations, frequently resulting in delayed diagnosis. The absence of any one symptom or sign rarely excludes a diagnosis.
- Obstruction of a hollow viscus, followed by distension, ischemia, and bacterial proliferation is a common pathophysiologic evolution in the infections of these organs.
- The potential toll on the elderly must be considered before ordering certain studies (e.g., renal failure from contrast, dehydration from colonoscopy).
- Peritonitis is always an absolute indication for surgery (with the exception of primary peritonitis). Advanced age and comorbidities should not preclude necessary surgery, but laparoscopy and minimally invasive adjuncts may be beneficial where feasible.

Intra-abdominal infections are a serious threat to the health of our rapidly enlarging geriatric population. However, the underlying causes – and means to diagnose those causes – can be markedly different than in younger patient subsets. In older patients, cholecystitis, diverticulitis, mesenteric ischemia, and intestinal perforation are more common, as shown in Table 1. However, atypical or incomplete clinical manifestations frequently lead to delayed diagnoses and complicated hospital courses. Elderly patients, for instance, are less likely to exhibit the classic “rebound and guarding” of peritonitis, leaving them at greater risk of misdiagnosis (2). Minimal leukocytosis is common. Dementia, delirium, confusion, and hearing disability can impede history-taking. Co-existing morbidities and associated poly-pharmacy confound the physical examination; peritonitis is more difficult to diagnose

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**Table 1** Different etiologies of intra-abdominal sepsis in patients over 65

Etiology	Percentage of patients, by age	
	>65	≤65
Appendicitis	28	61
Diverticulitis	28	6
Cholecystitis/cholangitis	24	10
Colon CA, sigmoid volvulus, and mesenteric ischemia	11	9

Adapted from (1)

in patients on corticosteroids or narcotics (3); tachycardia is masked by beta blockers, and fever may be suppressed by non-steroidal anti-inflammatory drugs. Finally, challenges of a social nature such as the inaccessibility of transportation, fear of relegation to a nursing home, and even elder abuse mean that elderly patients often present far later in the disease process with an accordingly altered symptomatology; however, the sword is double-edged. While accurate diagnoses may be more difficult among geriatric patients, delays in diagnosis are also met with far harsher penalties in terms of morbidity and mortality. Lastly, once a diagnosis is reached, the equally daunting task of assigning an appropriate therapy appears. This ageing population is more likely to require surgery, which is obviously not a benign intervention (4) and carries a unique cost-benefit ratio for each patient.

Therefore, the onus falls squarely on the physician to investigate judiciously the presentation of each geriatric patient and devise for him or her treatment strategy – whether medical, surgical, or minimally invasive – uniquely suited to improve both quantity and quality of life. Our chapter discusses broadly how this might be accomplished for appendicitis, diverticulitis, biliary disease, bowel obstruction, perforated peptic ulcer, and mesenteric infarction. The specifics of antibiotic therapy, along with other intra-abdominal infections such as pyelonephritis and *Clostridium difficile* colitis, are explored elsewhere in this text.

## Appendicitis

### *Epidemiology, Relevance, and Clinical Manifestations*

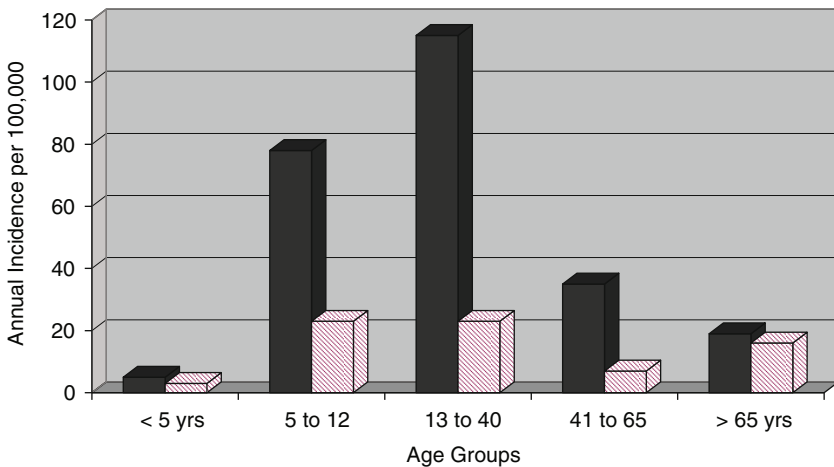
Appendicitis can serve as a model for the abdominal infectious process to which many other diseases are compared. The appendix is a “true” diverticulum arising during embryologic development from the cecum, and appendicitis is believed to result from obstruction of the narrow appendiceal inlet secondary to fecalith, lymphoid tissue enlargement or tumor. This, closed loop obstructive in turn, leads to a proliferation of intestinal flora causing distension of the lumen and proportionate necrosis of the wall as ischemia sets in.

Appendicitis accounts for 15% of all surgical emergencies in the elderly and is associated with a mortality rate of approximately 10% in the >70 subset (5); in

terms of clinical presentation, as with the very young, the very old range widely. The stereotypical presentation is one of fever, leukocytosis, nausea, vomiting, anorexia, and right lower quadrant pain migrating from the periumbilical region; however, one or all of these findings are commonly absent in geriatric patients. Studies show that only about one-third have fever (4) and that those over 80 years old are less likely to have right lower quadrant tenderness to palpation or a history of pain migration (6). Alternatively, older patients are more likely to have generalized pain, distension, decreased bowel sounds, and a palpable mass (4). Difficulty in definitively stating whether or not this atypical presentation causes delayed diagnosis is itself a result of delay or is indicative of an entirely different underlying pathophysiology, although all three theories have been set forth in the literature. Regardless, as depicted in Fig. 1, geriatric patients are far more likely to be misdiagnosed and treated later in their disease course, meaning that they are therefore much more likely to be perforated at the time of operation (6, 7). In patients age 65 and older, one large series revealed an incidence of 44% perforation (7).

### Diagnostic Tests

The attentive physician may establish a purely clinical diagnosis of appendicitis; however, for all the reasons noted above, a clinical diagnosis is not always feasible in an elderly patient, therefore, radiographic studies may be indispensable. The acute abdominal series – a convenient, efficient, and economic study generally obtained as a matter of course in the evaluation of any abdominal pain – is likely to yield little more than the nonspecific findings of ileus. Fecaliths and loss of the psoas shadow are occasionally detectable. The primary utility of plain film, however, is the expeditious



**Fig. 1** Age-specific incidence of nonperforated (black bars) and perforated (gray) appendicitis per year per 100,000 (adapted from Körner et al. (7))



exclusion of other differentials such as sigmoid volvulus. Computed tomography (CT) scanning with oral (PO) and intravenous (IV) contrast is viewed as the most accurate means of investigation. Findings suggestive of appendicitis on CT include pelvic free fluid, appendicoliths, abscesses, and an enlarged, edematous appendix with diameter  $>7$  mm that fails to fill with PO contrast. None of these findings are completely pathognomonic, though, and there exists considerable overlap with inflammatory bowel disease and terminal ileitis. Finally, ultrasound can also be helpful; it is particularly attractive in agitated or demented patients who may be unwilling to remain still for CT scan and patients with compromised renal function for whom IV contrast can be particularly harmful. A dilated, noncompressible appendix on ultrasound establishes a diagnosis with 85% sensitivity and 92% specificity; one may be fortunate enough to demonstrate appendicoliths and periappendiceal fluid as well (8). The disadvantage of ultrasound is that the pressure exerted by an ultrasound probe can be distressing to the patient with peritonitis; further, failing to locate an appendix on ultrasound provides no information whatsoever.

## ***Treatment***

The treatment of acute appendicitis is urgent appendectomy, which may be accomplished either open or laparoscopically. For such a routine relatively minor surgical procedure as appendectomy, it is uncertain whether a laparoscopic approach is likely to result in fewer complications for the elderly patient, although some studies seem to suggest it might (9, 10). Laparoscopy does seem to shorten hospital stays – a gain not to be underestimated in a population for whom prolonged bed rest is particularly debilitating (9). The special allure of laparoscopy, however, lies in its ability to assess the entire abdomen in those instances where diagnosis may be question. Of course, these advantages must be weighed carefully against the dangers of carbon dioxide pneumoperitoneum in patients with cardiovascular or pulmonary disease. Moreover, elderly patients are more likely to have had previous surgery, leaving them with intra-abdominal adhesions, which make laparoscopy difficult or even impossible. Regardless of the approach, preoperative antibiotics are indicated for all patients, as are postoperative antibiotics until the resolution of fever in those patients with perforation.

## **Diverticulitis and Diverticulosis**

### ***Epidemiology and Clinical Relevance***

Since 1900, the introduction of the rolling mill in Western civilization has resulted in low-fiber diets and an epidemic of colonic diverticulosis. Unlike the appendix, colonic diverticula are false, arising from herniation of mucosa and submucosa through the muscle of the bowel wall most commonly in the sigmoid. The

prevalence of diverticular disease in Western countries ranges from around 5% at age 40 to as high as 65% at 65 (11). As many as one-quarter of those affected will develop symptomatic diverticulitis secondary to obstruction, which may range from micro-perforation to frank purulent or even fecal peritonitis, with or without a disturbing myriad of complications including chronic fistulas and obstruction. Patients with chronic obstructive pulmonary disease, coronary artery disease, and end-stage renal disease are far more likely to have such complications (12). Not surprisingly, the mortality associated with perforation in an older patient approaches three times that of a younger patient (1, 13).

### ***Clinical Manifestations***

Given the similarities in underlying pathophysiology, it is easy to see why acute diverticulitis frequently presents as almost a left-sided appendicitis. A marked redundancy of the sigmoid colon and generous mesentery, however, can lead to some surprising variations in pain location. Like appendicitis, patients frequently complain of decreased appetite and nausea and may exhibit physical findings such as low-grade fever, mild abdominal distension, left lower quadrant tenderness, a palpable mass, and leukocytosis or left shift. Rectal examination may elicit tenderness, and 25% of patients will have stools positive for occult blood.

### ***Diagnostic Tests***

The acute abdominal series should not to be overlooked, as it may reveal to the astute investigator diagnostic findings such as air in the bladder (implying a colovesicular fistula) or, more importantly, free air in the peritoneal cavity. However, with 93% sensitivity and 100% specificity, the study most apt to yield an accurate diagnosis of diverticulitis is again CT with PO and IV contrast. Barium enema may also be employed, but it fails to depict complications such as abscesses that are rarely missed by the wide-ranging image of CT. Findings suggestive of diverticulitis on CT scan include diverticula themselves, stranding of pericolonic fat, thickened bowel wall to 4 mm, and enhancing fluid collections. Due to the increased risk of perforation, colonoscopy should be avoided during the acute attack but is often pursued several weeks later to explore the extent and severity of the underlying diverticulosis and to screen for any coexisting tumors.

### ***Treatment***

The initial treatment of uncomplicated acute diverticulitis is conservative medical therapy consisting of bowel rest, fluid resuscitation, and antibiotics. Once resolution

of the inflammatory process is appreciated, the patient should be started on a high-fiber diet.

Several clinical scenarios, however, may prompt a more definitive treatment. Peritonitis, of course, and often obstruction are surgical emergencies. Abscesses may be down-staged with percutaneous CT-guided drainage, allowing for elective resection of the underlying disease. Likewise, antibiotics alone are little more than a temporizing measure when treating colovesicular and other fistulas. Finally, a second bout of diverticulitis in the same patient implies that the disease process will continue to recur and should be managed with elective surgery at a later date.

Surgery, in addition to treating the particular complication, entails resecting en masse the entire colonic segment affected by diverticulosis, which typically implies a sigmoidectomy. The re-creation of intestinal continuity is then a question of some debate. Although an end colostomy and distal Hartman Pouch was, at one time, favored in the setting of acute inflammation for fear of anastomotic leakage, primary anastomosis, with or without a diverting ileostomy, is now widely accepted even for emergent cases. The question of whether or not to leave a stoma is highly individualized and should take into consideration the toll it is likely to take on a specific patient's quality of life. Is the risk of additional surgery to reverse the stoma prohibitively high? Does malnutrition contribute unduly to the likelihood of anastomotic breakdown? Are there pre-existing comorbidities such as chronic diarrhea, dementia, or paraplegia that may make the ease of stoma maintenance desirable (14)? Regardless of which procedure is ultimately settled upon, special consideration should also be given to closing with retention sutures, given the higher incidence of postoperative wound infection and resulting fascial dehiscence in geriatric patients (13).

## **Cholecystitis and Biliary Disease**

### ***Epidemiology and Clinical Relevance***

One-third of all patients older than 55 that are seen/treated in the emergency department for abdominal pain are found to have biliary tract disease (4); in fact, the most common cause of intra-abdominal infections in the elderly is acute cholecystitis, and the number of cholecystectomies performed on this population is increasing. Cholelithiasis underlies 95% of acute cholecystitis, with the other 5% termed acalculous cholecystitis. The incidence of cholelithiasis increases with age, ranging from 25 to 40% during the seventh decade of life to over half of those in their eighth decade. While still more common in women, the discrepancy in female:male incidence diminishes from 3:1 in younger adults to 3:2 in those older than 50. Men are more likely to have complicated cholecystitis, so perhaps it is not coincidental that 20% of those older than 50 also have serious complications such as gangrenous cholecystitis, gallbladder perforation, and even cholecystoenteric

fistula resulting in gallstone ileus (obstruction at the ileocecal valve) or Bouveret Syndrome (duodenal obstruction) (1, 15).

### *Clinical Manifestations*

In the elderly, therefore, biliary disease should be considered foremost in the differential diagnosis of upper abdominal pain. The disease is thought to occur when a stone or mass obstructs outflow from the cystic duct. Pain typically occurs in the right upper quadrant and epigastrium with radiation to the back, flank or scapula and is often exacerbated by eating. Nausea, vomiting, and fever are common complaints. On physical examination, palpation of the right upper quadrant stimulates tenderness, which in the setting of peritoneal inflammation is specifically manifest as Murphy's sign: inspiratory arrest with deep palpation. Very severe chronic inflammation can lead to omental segregation of the diseased area and a corresponding palpable mass on examination. Scleral icterus or frank jaundice should raise suspicion for choledocholithiasis or the more ominous cholangitis, especially when the remaining members of Charcot's Triad (fever, right upper quadrant pain, and jaundice) or Reynold's Pentad (Charcot's Triad plus altered mental status and hypotension) are present. On laboratory studies leukocytosis and/or left shift are common; bilirubinemia and elevated alkaline phosphatase may indicate involvement of the duct. Amylase and lipase should also be checked, as significant elevations in these markers prompt concern for superimposed gallstone pancreatitis.

### *Diagnostic Tests*

When biliary disease is suspected, ultrasound is by far the study of choice, with a 95% sensitivity for the detection of gallstones. Sonographic findings indicative of cholecystitis include a thickened gallbladder wall (>4 mm), edematous wall or the so-called "double wall sign," pericholecystic fluid, and, in the setting of choledocholithiasis, a dilated common bile duct (>1 mm per decade of life, or >7 mm). A sonographic Murphy's sign or pain elicited by the pressure of the ultrasound probe while visualizing the gallbladder, is perhaps the most accurate indication of cholecystitis. In those patients with equivocal findings, a hepatobiliary iminodiacetic acid (HIDA) scan is 100% sensitive and 95% specific for acute cholecystitis (16). The radio-labeled tracer is taken up by the liver and excreted in the bile but cannot physiologically reflux into an obstructed cystic duct, thus rendering the gallbladder invisible via this imaging modality in patients with cholecystitis. In addition, because HIDA scan evaluates biliary function in real time, pairing this study with an injection of cholecystokinin can demonstrate a low gallbladder ejection fraction (<50%). This favors a diagnosis of biliary dyskinesia, where many symptoms of chronic cholecystitis are present, but the signs are frustratingly absent.

## ***Treatment***

Surgery is the only definitive treatment for cholecystitis and symptomatic cholelithiasis. Unfortunately, complications are manifold in elderly patients undergoing cholecystectomy: one large database study showed a 12% increased risk of local complications and 30% increase in systemic complications for every 12 years of life (17). Complications range from common bile duct injury to cerebrovascular accident, pulmonary edema, and myocardial infarction. Nonetheless, in the past few decades, an explosion of adjunct therapies and surgical techniques has rendered surgery more and more appropriate for even the extremely elderly. Paramount among these, of course, is the advent of laparoscopic cholecystectomy. Morbidity and mortality are approximately halved by the laparoscopic approach, with mortality approaching a very acceptable 0–1% even in patients over 70 with an American Society of Anesthesiologists (ASA) score >3 (18). However, laparoscopic cholecystectomy is hardly a panacea; it behooves the surgeon to bear in mind the relatively high rate of conversion to open in geriatric patients and to prepare accordingly. On the one hand, for patients with a serum bilirubin >3 mg/dl who might benefit from a period of medical optimization prior to surgical intervention, endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy can buy time and is superior to antibiotics alone. On the other hand, avoiding cholecystectomy altogether after ERCP incurs a prohibitively high likelihood of emergent cholecystectomy and all its attendant risks (19, 20). ERCP is also indicated emergently for cholangitis and either pre- or postoperatively for choledocholithiasis. Unstable patients, such as the classical intensive care unit (ICU) patient with acalculous cholecystitis, are generally best served with bedside cholecystotomy tube under ultrasound guidance until surgery can be safely undertaken.

## **Bowel Obstruction**

As with appendicitis, diverticulitis, and cholecystitis obstructing any part of the small or large bowel can result in gangrene and perforation. Causes of bowel obstruction that are common among the elderly include diverticulitis as mentioned above as well as sigmoid volvulus, acute colonic pseudo-obstruction (ACPO) or Ogilvie Syndrome, and colon cancer. Less likely culprits such as gallstone ileus and femoral hernias should also be kept in mind.

## ***Sigmoid Volvulus***

Sigmoid volvulus is 20 times more common in patients over 60 years of age. Although volvulus may also occur in the cecum, the sigmoid is by far the most frequent location. The typical patient is one for whom a variety of factors – low

fiber diet, paraplegia, chronic illness, neurologic disorders, or anticholinergic medications – have conspired to create a state of persistent constipation. It makes sense that this backlog of stool volume would, in turn, stimulate redundancy of the sigmoid, thus raising the likelihood that it will twist upon its mesentery. The typical early presentation is acute onset of colicky diffuse abdominal pain, distension, obstipation, and sometimes feculent emesis. When strangulation sets in, patients develop peritoneal signs along with an overall septic picture, including fevers, leukocytosis and/or left shift, and hypotension.

Plain abdominal films are extraordinarily helpful in diagnosing this particular disease process, as they characteristically depict a dilated sigmoid “bird’s beak” directed at the site of obstruction. A barium enema can also be used to reveal a similar tapering of contrast proximally, but it is feared to cause perforation in a bowel already strangulated. CT may show a “whirl sign” where the mesentery contorts, or free fluid, stranding, and, if ischemia is present, air in the intestinal wall.

In sigmoid volvulus, as elsewhere, peritoneal signs and other evidence of gangrene require emergent laparotomy and resection. Mortality in this instance approaches 50–70%. Uncomplicated volvulus may be handled in the acute setting with colonoscopic decompression and rectal tube placement, but a high rate of recurrence (approximately 55–90%) dictates the patient later undergo elective sigmoidectomy. For these patients, laparoscopic sigmoidectomy is an especially tempting option.

### ***Acute Colonic Pseudo-Obstruction, or Ogilvie Syndrome***

ACPO, also known as Ogilvie Syndrome, typically preys as a comorbidity on those patients who are already direly affected by pre-existing illness. The most common risk factors include heart disease, sepsis, trauma, and surgery elsewhere in the body. Patients are often on multiple medications, including, notably, narcotics and have electrolyte abnormalities such as hyponatremia. How these relate to the suspected pathophysiology of ACPO – an underlying imbalance of sympathetic and parasympathetic impulses to the large bowel – is unclear, but the end product is an impressively dilated large bowel on radiologic studies, paradoxically without actual mechanical obstruction. The cecum is the portion of large bowel with the greatest diameter, and therefore, by LaPlace’s law, the portion most drastically affected by the resulting tension.

Conservative treatment consists of bowel rest, intravenous fluids, correction of electrolyte abnormalities, increasing physical activity where possible, and discontinuing offending medications. Non-operative treatment alone will bring about spontaneous resolution in 85% of patients at just 3 days (21). Above 12 cm of cecal diameter, however, concerns for impending gangrene and perforation (which has 50% mortality) compel urgent intervention, as does duration of symptoms >6 days (22). Peritonitis and gangrene mandate emergent laparotomy and resection. As with sigmoid volvulus, patients without gangrene may experience relief from

decompression and rectal tube placement via colonoscopy; this maneuver is successful in 70% of patients. Neostigmine, a reversible acetylcholinesterase inhibitor, is another attractive alternative, producing sustained resolution in at least two-thirds of patients, and is especially effective in the elderly and females (21, 23). Patients who respond only partially or temporarily can receive repeat doses. Nonetheless, physicians must exercise keen judgment when selecting prospective patients for this therapy because a multitude of comorbidities exacerbated by such a powerful cholinergic is a definite risk. Cardiac arrhythmias, relative hypotension (systolic pressure in the 90s), bronchospasm, and renal insufficiency are all contraindications to the use of neostigmine. If less-invasive therapies like colonoscopy and neostigmine fail or are contraindicated, surgical decompression and placement of ostomy (or percutaneous cecostomy in patients unfit for surgery) may be necessary even in the absence of gangrene. A treatment algorithm for ACPO incorporating all these therapies in proposed in Fig. 2.

## *Colon Cancer*

In the elderly, malignancy is the most common cause of large bowel obstruction (4). Cancer of the colon and rectum is the second most common cancer in western civilization with an incidence of 150,000 new cases each year. Approximately three-fourths of tumors occur in those 65 years and older and, when the tumors are sufficiently large, they may result in obstruction and even perforation in up to 10% of patients. The resulting peritonitis then prompts emergent surgery, and the underlying diagnosis is reached intra-operatively upon direct inspection. Perforation is the most deadly complication of colon cancer, with an operative mortality of 33% (1); those older than 70 do particularly poorly (24). Moreover, since perforation is almost always the byproduct of a very advanced cancer, even those that do well in the immediate postoperative period face a dismal long-term prognosis. Therefore, although complete oncologic resection is the only definitive treatment, bypass procedures and stomas are acceptable for both temporizing and palliative purposes.

As with most other cancers, the key to successful treatment of colon cancer is early detection, thus ideally obviating the possibility of obstruction and perforation entirely. Colon cancer – like breast, cervical, and prostate cancers – can be screened for using relatively noninvasive means (e.g., in the case of colon cancer, flexible sigmoidoscopy and colonoscopy). This is undoubtedly most beneficial to the otherwise healthy 50 year old, but what is the practical utility of discovering a minuscule, slow-growing cancer in an 80 year old with two or three pre-existing conditions? Most patients would gladly forgo the discomfort of a procedure unlikely to help them. In addition, dehydration, electrolyte imbalance, and even perforation secondary to both the bowel preparation as well as the actual colonoscopy itself are not unheard of in the elderly population. It is generally accepted that colon cancer screening benefits only those with a future life expectancy of 5 years or more. On average, an 81-year-old patient can expect to live an additional 11.2

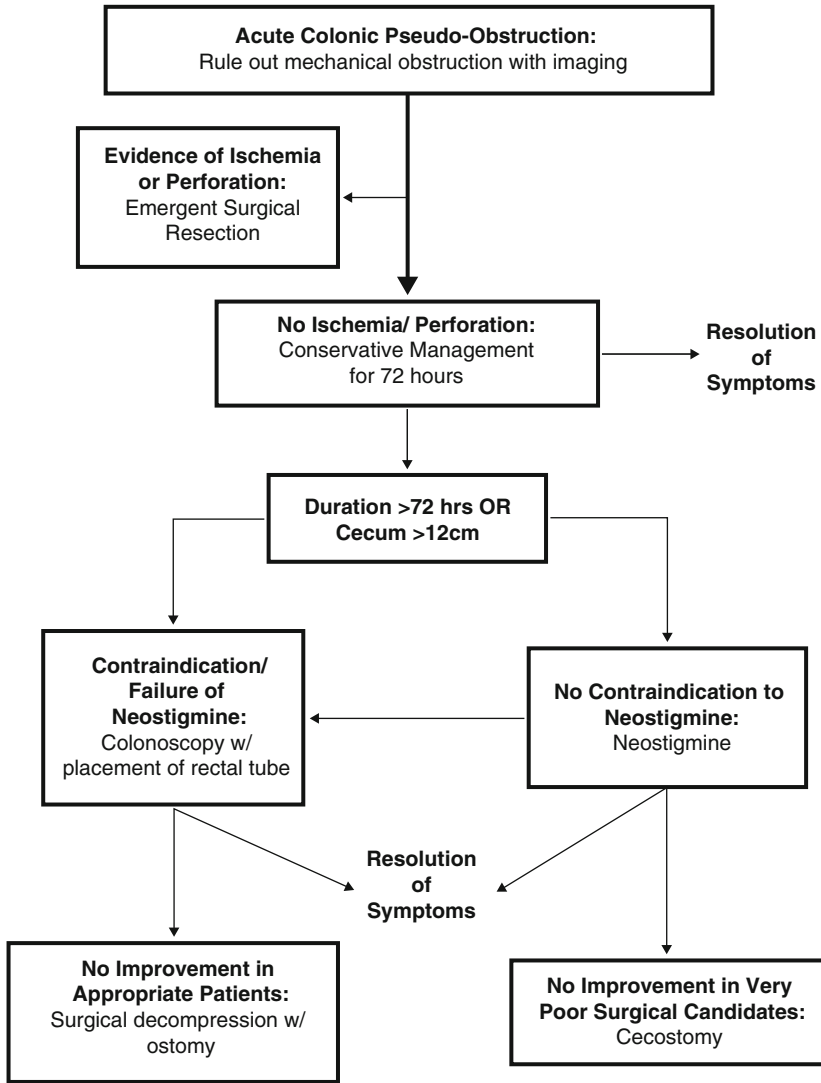


Fig. 2 Treatment algorithm for acute colonic pseudo-obstruction (Ogilvie Syndrome)

years, making screening a wise choice. However, that same patient with the combined comorbidities of cerebrovascular disease, coronary artery disease, and chronic obstructive pulmonary disease may only live an average of four more years (25, 26). It is clear that the decision to screen or not to screen in the elderly is a highly individualized one, dictated by each patient's unique history.



## **Perforated Peptic Ulcer**

### ***Epidemiology and Clinical Relevance***

A total of 16% of abdominal pain in elderly patients can be attributed to peptic ulcer (4). In part, this percentage is likely due to the prevalence of certain risk factors amongst geriatric patients, including the chronic use of corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDS). Ethanol abuse and infection with *Helicobacter pylori* are additional risk factors present in certain patients. Finally, since sepsis, ventilatory dependence, burns, and head trauma also predispose to ulcer development, the critically ill are at especially high risk. The modern adoption of routine pharmacologic prophylaxis in ICUs throughout the nation underscores the graveness of this threat as well as our recent successes in preventing it.

### ***Clinical Manifestations***

Unlike perforation in the other portions of the gastrointestinal (GI) tract discussed above, a perforated peptic ulcer is not usually secondary to obstruction; however, it is likely that ischemia still plays a role in the pathogenesis. Decreased blood flow may be secondary to septic shock or a side effect of NSAIDS inhibiting the prostaglandin-mediated vasculature of the gastric mucosa. The end result of perforation is, as elsewhere, a weakened and then perforated viscus wall releasing contamination into the heretofore sterile peritoneal cavity.

Unfortunately, many patients will not present with symptoms before reaching this disheartening endpoint. Approximately 30% of patients age greater than 60 with uncomplicated peptic ulcer disease deny having abdominal pain (4). The advent of perforation, then, is heralded by an abrupt onset of severe epigastric pain and peritoneal signs. Leukocytosis and serum amylasemia quickly ensue.

### ***Diagnostic Tests***

Clinical peritonitis circumvents the need for additional studies, as the physician is already obligated to operate. Prior to surgery, upright plain films may demonstrate free air but only in about 50% of patients (4). CT is a more sensitive study for this purpose and can also demonstrate free fluid, stranding, and other markers of inflammation. Barium swallows are convenient for diagnosing ulcers, but barium itself can be corrosive outside the GI tract and is therefore contraindicated if perforation is suspected. Water-soluble contrast is worth considering. Likewise, upper endoscopy in the setting of perforation risks artificially worsening pneumoperitoneum and traumatically exacerbating injuries.

To aid diagnosis in the nonemergent setting, exposure to *H. pylori* can be detected using routine serology. Ongoing *H. pylori* infection is demonstrated via the urease breath test or the presence of stool antigens.

## ***Treatment***

Surgical repair of perforated peptic ulcers is a foregone conclusion, but the specific repair itself can take many different forms according to the location of the ulcer, the individual needs of the patient, and the surgeon's preference. These include primary closure, Graham patch with omentum, and the less frequently performed partial gastrectomy or antrectomy. Vagotomy and pyloroplasty remain useful techniques. It is generally agreed that repair of a gastric ulcer should incorporate resection of the lesion for histologic analysis, as the risk of malignancy is not negligible in these instances. The addition of an acid-reducing procedure such as vagotomy to the repair reduces ulcer recurrence (27, 28).

Pharmacotherapy plays a substantial role in the prevention and treatment of this disease. Wherever possible, offending drugs such as corticosteroids and NSAIDs should be discontinued. *H. pylori*, if present, must be eradicated with antibiotics. Sucralfate, histamine (H<sub>2</sub>) blockers and proton pump inhibitors (PPIs) are all then commonly employed for both prophylaxis and treatment. Although debate continues regarding the respective superiority of individual drugs, it is worth remembering that H<sub>2</sub>-blockers can cause delirium, and, rarely, thrombocytopenia in the elderly or critically ill. For such patients, a PPI may be the more appropriate choice.

## **Acute Mesenteric Infarction**

### ***Epidemiology and Clinical Relevance***

Acute mesenteric infarction may lead to catastrophic intra-abdominal infection. Patients greater than 70 years of age have a 43% mortality, which is 3½ times the relative risk of younger patients, even after controlling for a longer ischemic time on average (29). Arterial emboli to the superior mesenteric artery cause 30% of cases. These emboli usually originate from the mural thrombus of an infarcted left ventricle or fibrillating left atrium. By contrast, in situ thrombus of the artery occurs in 25% of patients and is generally the result of atherosclerotic narrowing at the vessel's take-off point. Other less common causes of acute mesenteric infarction are thrombosis of mesenteric veins, aortic dissection, and various vasculitides.

## *Clinical Manifestations*

Mesenteric vascular occlusion leads to necrosis of villi, mucosal sloughing, ulceration, and bleeding. Pain described as “out of proportion to the physical examination,” meaning intense but without peritoneal or localizing signs, is a hallmark of mesenteric ischemia. The pain is severe, diffuse, and, as shown in Table 2, associated with nausea, fever, tachycardia, diarrhea, and/or constipation (29). Unfortunately, this constellation of symptoms is often confused with gastroenteritis. As little as one-fourth of patients will have stool positive for fecal occult blood (4). Acute thrombus (as opposed to embolus) is occasionally foreshadowed by a history of so-called “intestinal angina,” or “food fear.” Other root pathologies such as dissection will, of course, have their own defining characteristics. Regardless, late in the course of disease a common clinical presentation of peritonitis and fulminant sepsis too often materializes. Leukocytosis and/or left shift, hyperamylasemia, increased serum lactate, and acidosis may be manifest only in extremis. In particular, lactate >2, white count over 18,000/mm<sup>3</sup>, and symptoms for more than 12 h portend a significantly higher mortality (29).

## *Diagnostic Tests*

Reaching a firm diagnosis of mesenteric infarction can be an intimidating undertaking, as no single study will settle the question conclusively and radiologic findings, as with laboratory values, often arise too late to prevent substantial mortality. Acute abdominal series are usually unremarkable early in ischemia, but as the disease progresses, may show evidence of obstruction (dilated small bowel and air-fluid levels), edematous bowel wall (“thumbprinting” and thickening), free air and, rarely, pneumatosis intestinalis or air in the intrahepatic portal venous system. CT scans are useful for uncovering these same findings with greater detail and therefore

**Table 2** Presenting symptoms/signs in 72 patients with acute mesenteric ischemia

Presenting symptom/sign	No. of patients	%
Pain	69	96
Nausea/vomiting	40	56
Peritonitis	26	36
Diarrhea	22	31
Heart rate >100 bpm	22	31
Arrhythmia	20	28
Fever	15	21
Hematemesis	13	18
Constipation	6	8
Shock	4	6

Adapted from (29)

*bpm* beats per minute

sensitivity. Fine cuts on CT with contrast may even detect the offending filling defect. The convenience of this latter modality, however, must be weighed against the dangers of using a nephrotoxic agent in an elderly patient already at risk for developing acute renal failure in the sepsis to come. The same must be said of formal angiography.

## ***Treatment***

Where peritoneal signs are present, exploratory laparotomy is warranted. In patients for whom radiographic and laboratory results are equivocal, but clinical suspicion remains high, the occasional negative or nontherapeutic laparotomy must be borne in an effort to intervene suitably early in the disease process. Men and the elderly, however, are far more likely in this scenario to have positive findings of mesenteric ischemia on laparotomy, arguing that a lower threshold to operate might be appropriate in these patients (30). The aim of surgery is twofold: to resect necrotic bowel (with or without a stoma) and to reperfuse bowel which is ischemic but salvageable. This second aim is certainly the more lofty and may entail heparinization as well as bypass graft, venous patch, embolectomy and operative techniques that the vascular surgeon has at his/her disposal. A planned “second-look” laparotomy the following day may be in order to determine the success of these efforts and resect any remaining areas of necrosis which have declared themselves in the interim. Antibiotics are, of course, a necessary companion to surgery.

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# Infectious Diarrhea

Manie Beheshti and W. Lance George

## Key Points

- The mechanisms of disease production by enteric pathogens include mucosal adherence, mucosal invasion, and the effect of toxins and destruction of absorptive cells.
- Clinical syndromes of infectious diarrhea include food poisoning, viral gastroenteritis, diarrhea in the returning traveler, community-acquired infectious diarrhea, *Clostridium difficile* infection, and subacute to chronic diarrhea due to parasitic diseases.
- Bloody diarrhea in an afebrile patient should raise suspicion for enterohemorrhagic *Escherichia coli* infection (i.e., *E. coli* O157:H7).
- Outbreaks of vomiting and diarrhea in the setting of communal living are strongly suggestive of norovirus infection.
- Diarrheal disease after recent antimicrobial therapy is strongly suggestive of *C. difficile* infection.

## Introduction

Viral, bacterial, and parasitic gastrointestinal infections are common causes of morbidity and mortality in elderly patients; many bacterial and parasitic enteric pathogens are treatable. A careful assessment of risk factors and a stepwise approach to diagnosis and treatment are important in the management of infectious diarrhea. Due to the substantial communicability of some pathogens (e.g., *C. difficile*, norovirus, and *Shigella species*), infection control management is essential in both

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acute and chronic healthcare facilities. Over the past several years, *C. difficile* infection (CDI) has become more prevalent and has been noted to cause increased in-hospital morbidity and mortality. Epidemiology, pathogenesis, clinical features, diagnostic methods, and therapeutic considerations of common enteric pathogens in the elderly are discussed here.

## Epidemiology and Clinical Relevance

In all age groups, infectious diarrhea is a leading cause of morbidity and mortality worldwide. Due to the highly infectious nature of some pathogens, specific measures for control and prevention of spread are of great importance. Approximately 211–375 million episodes of diarrheal illness occur annually in the United States accounting for approximately 73 million physician visits, 1.8 million hospitalizations, and 3,100 deaths; total costs are approximately \$23 billion, including costs for healthcare and loss of productivity (1, 2).

The impact of diarrheal disease in older patients is particularly noteworthy. In one population study in the United States, 78% of deaths were attributed to diarrhea occurred in adults older than 55 years (3), while in other studies 85% of all deaths from diarrhea occurred in those older than 80 years (4, 5). A 3% fatality rate has been described in patients older than 80 years of age (4).

Infection is usually acquired by fecal–oral spread or ingestion of contaminated food products. Food contamination can occur by a variety of mechanisms. During the growing process, vegetables may become contaminated in nature; a common example is the contamination of lettuce and spinach by toxigenic *E. coli* O157:H7. Ingestion of such food products without prior cooking can lead to enteric infection. Contamination may also occur during food processing or production; examples of apparent contamination during food production include the occurrence of *Salmonella* species in peanut butter or of toxigenic *E. coli* O157:H7 in ground beef. In the latter example, contamination happens through cattle being colonized by the organism while living, with the resultant contamination of the carcass occurring during slaughter or dressing of the beef. Contamination of poultry meat by *Campylobacter jejuni* (and other enteric pathogens) occurs by a similar mechanism. Many enteric pathogens can be spread by infected food handlers during food preparation, particularly when there are lapses in hand-washing practices and other safety measures. Fecal–oral spread may occur directly from patient-to-patient, by contamination of inanimate objects in the environment, or from failure of healthcare workers to observe hand hygiene.

Infection control in acute and chronic healthcare settings is of utmost importance in preventing the spread of highly transmissible pathogens such as *C. difficile*, *Shigella* species, and norovirus. The most effective, economical, and reasonable intervention is appropriate hand hygiene; unfortunately, lapses in hand hygiene are common. Of note, alcohol-based hand cleansing gels are considered by some experts to be less effective than soap and water in preventing the spread of *C. difficile*



because alcohol-based hand cleansing gels do not kill spores. In acute healthcare facilities, patients with suspected or documented enteric infections should be isolated in a single room and personal protection equipment (i.e., gloves and isolation gowns) should be used. Patient care areas should be properly cleansed with appropriate disinfectants (e.g., 1:10 bleach dilution). In the case of norovirus infection, the Centers for Disease Control and Prevention (CDC) recommend that infected food handlers should not handle food until 2–3 days after they have recovered from their illness (6). Hygienic considerations include adequate sanitation during preparation and food storage. In many states, infection by enteric pathogens is reportable. In cases of localized or facility-based outbreaks, the local or state health departments should be contacted for assistance with rapid pathogen identification and assistance with control of spread of infection.

Because infections occur as a consequence of oral ingestion of a pathogen, natural barriers of the host to infection such as gastric acidity, mucus, and the normal bacterial flora of the large bowel are important host factors. Hypochlorhydria or achlorhydria resulting from aging, disease, medications, or gastric surgery blunts or eliminates this naturally protective acidic host barrier. As a method of expelling pathogens and toxins, intestinal motility is an important host defense; the use of antimotility agents and narcotics for pain relief has been linked to complications of infectious diarrhea, including prolonged fever, prolonged shedding of the pathogen, and increased risk of complications of infections such as a heightened predisposition to the development of the hemolytic-uremic syndrome in enterohemorrhagic *E. coli* infection or the development of toxic megacolon in the case of *C. difficile* infection. The importance of the host's normal flora has also been well documented. Use of antimicrobials agents causes disruption of the normal intestinal flora, which possesses an ill-defined quality, often termed colonization resistance; antimicrobial-induced loss of colonization resistance results in an increased risk of infectious diarrhea, particularly that caused by *C. difficile*. With waning adaptive and humoral immunity of the intestinal tract, the host may also be less able to abort or ameliorate infection.

### ***Pathobiology of Infectious Diarrhea in the Elderly***

Diarrhea can be defined as a decrease in the consistency of stools accompanied by an increase in the frequency of bowel movement to three or more daily (2). Diarrhea, of course, can be caused by infectious agents (Table 1) but systemic illness (Table 2) and medications (Table 3) are other important considerations.

The pathogenesis of infectious diarrhea involves both host and microbial factors (7). Immunosenescence, a waning host immune response with aging, which includes a minimal decline in innate immunity, decreased humoral or antibody response, select neutrophil dysfunction, and impaired cell-mediated immunity appears to play an important role (8). Additional factors likely to affect the elderly include the increased infectious risks associated with communal living and a decrease in gastric acid production related to medications such as histamine receptor

**Table 1** Enteric pathogens in adults

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Viruses
Norovirus (Norwalk virus; Norwalk-like virus)
Rotavirus
Astrovirus
Adenovirus
Bacteria
<i>Shigella</i> species
<i>Salmonella</i> species
<i>Campylobacter jejuni</i>
Other <i>Campylobacter</i> species
<i>Escherichia coli</i>
<i>Clostridium difficile</i>
<i>Vibrio cholerae</i>
Other <i>Vibrio</i> species
<i>Aeromonas</i> species
<i>Yersinia enterocolitica</i>
Protozoa
<i>Cryptosporidium</i>
<i>Giardia lamblia</i>
<i>Entamoeba histolytica</i>
<i>Microsporidium, isospora, cyclospora</i> (immunocompromised patients)

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**Table 2** Examples of non-infectious causes of diarrhea in the elderly

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Medications (see Table 3)
Fecal impaction with “overflow”
Irritable bowel syndrome
Inflammatory bowel disease (i.e., ulcerative colitis and Crohn’s disease)
Lactase deficiency
Thyrotoxicosis
Systemic sclerosis
Whipple’s disease
Amyloidosis of the bowel
Secretory diarrhea due to tumors secreting gastrointestinal peptides
Lymphoma
Chronic pancreatitis
Celiac disease
Mesenteric Ischemia
Diverticulitis
Colonic carcinoma
Diabetic enteropathy

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Adapted from (38)

blockers or proton pump inhibitors, or diseases associated with hypo- or achlorhydria, more aggressive cancer treatment in the elderly, and an apparent increase in the contamination of the food supply in recent years.

Various microbial factors play a role in the mechanism of infectious diarrhea (7). Adherence of bacteria to the bowel mucosal surface such as that which occurs with enteropathogenic *E. coli*, may allow a pathogen to gain a foothold in order to proliferate and to provide proximity of the enterotoxin to the intestinal mucosal

**Table 3** Medications associated with non-infectious diarrhea

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Antimicrobial agents (nonspecific diarrhea) <sup>a</sup>
Cancer chemotherapeutic agents
Cardiovascular drugs
Antiarrhythmics
Antihypertensives
Diuretics
Cholesterol-lowering agents
Central nervous system drugs
Antiparkinsonism drugs
Antianxiety drugs
Gastrointestinal drugs
Antiulcer drugs
Cathartics, lactulose
Bile salts
5-Aminosalicylic acid compounds
Miscellaneous
Nonsteroidal anti-inflammatory drugs
Theophylline-containing drugs
Cochicine

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Adapted (38)

<sup>a</sup>See text

cells. Invasion of mucosal cells triggers an inflammatory response that can lead to cell death. *Shigella* is a prototypical example that causes clinical findings typical of invasive disease (i.e., fever, abdominal cramps, malaise, and dysentery). Bacterial toxins can elicit various host responses: cytotoxins induce an inflammatory colitis by destruction of colonic mucosa such as that which occurs with *C. difficile*, whereas enterotoxins stimulate active electrolyte secretion by the mucosal cells, resulting in large-volume, watery stools. For example, in *Vibrio cholerae* infection, the intestinal mucosa retains its morphologic integrity, but the small bowel mucosal cells are induced to secrete fluid and electrolytes; the large volume of fluid reaching the colon overwhelms the bowel's reabsorptive capacity, resulting in profuse watery diarrhea that can lead to life-threatening dehydration. The direct injury or destruction of the intestinal absorptive cells by organisms such as rotavirus and norovirus lead to disruption of absorptive fluid balance and decreased production of digestive enzymes.

## Clinical Manifestations, Diagnostic Evaluation and Tests, and Treatment

### *History*

The history can often help in guiding the initial diagnostic evaluation. Assessments should be made with regard to immunosuppression, food exposure and travel history, including potential outbreak exposures, medication use (Table 3), particularly antibiotics, fever history and duration, and nature of the diarrhea (i.e., volume,

frequency, tenesmus, and presence of blood or mucus in stool), and weight loss. Awareness of outbreak exposure (e.g., norovirus in a healthcare facility or on a cruise ship) or travel to endemic areas provides information vital for diagnosis. Food history should include a thorough assessment of eating and dietary habits, especially ingestion of uncooked, undercooked, or improperly cooked or stored foods.

Symptomatic clues may aid in the understanding of the mechanism of diarrhea and hence provide early clues as to its pathogen. Emesis, as the predominant symptom, suggests viral gastroenteritis or toxin-mediated food poisoning such as that caused by *S. aureus*, *Clostridium perfringens*, or *Bacillus cereus* (9). Invasion of the bowel mucosa may lead to fever as a major finding (i.e., *Shigella* species, *Salmonella* species, *Campylobacter* species, rotavirus, and norovirus). Passage of a small number of voluminous stools suggests diarrhea of small bowel origin, as is seen in infections with *V. cholerae*, enterotoxigenic *E. coli*, *Giardia lamblia*, or early shigellosis. Many small volume watery stools with fecal urgency or with blood or mucus in the stool suggest large bowel involvement and possibly colitis, as seen in infection due to *Shigella* species, *Salmonella* species, *C. jejuni*, *Entamoeba histolytica*, or *C. difficile*.

### ***Physical Examination***

The physical examination is usually not of value with regard to the specific etiologic agent. However, assessment for dehydration, a significant cause of morbidity in the elderly, and for incipient or early bowel perforation is essential. Among findings that suggest dehydration are orthostatic hypotension, dry mucous membranes, skin tenting, and alteration in mentation, especially acute delirium in older persons. The abdominal examination may provide important clues aiding in the diagnosis, although elderly persons may exhibit minimal findings on examination. While common nonspecific symptoms such as mild, diffuse tenderness may be present without guarding or rebound, the presence of marked tenderness or early peritoneal signs are suggestive of impairment of bowel wall integrity, as may sometimes occur with severe infection due to *C. difficile* or *Salmonella typhi*. Occasionally, the clinical presentation of infection by *Yersinia enterocolitica* or *C. jejuni* infection can mimic acute appendicitis. A history of bloody diarrhea should lead to the suspicion of enteroinvasive pathogens, including *Shigella* species, *Salmonella* species, *C. jejuni*, or enterohemorrhagic *E. coli*; similarly, the passage of blood and mucus suggests a dysentery-like picture consistent with shigellosis or amebiasis.

### ***Diagnostic Tests***

Along with a physical examination to evaluate for dehydration and assess severity of illness, additional basic laboratory tests such as electrolyte studies and complete blood count may be helpful depending on the severity of the diarrhea (2). Modalities aiding in the evaluation of infectious diarrhea include stool examination for white

blood cells, stool culture, assessment for parasites and their ova, and toxin detection. If the test is available, the detection of fecal leukocytes can be useful in suggesting the need for bacterial culture of feces. In addition to identifying a specific pathogen, stool cultures can be of epidemiologic importance. Although of relatively low yield, it is reasonable for these studies to be routinely performed, particularly when diarrhea is acquired in the community and the illness is more than trivial. For example, in a 1994 outbreak of more than 220,000 infections due to *Salmonella enteritidis*, detection of the organism from cases in one region of Minnesota led to the recall of contaminated ice cream thereby terminating the epidemic (2). In patients who develop diarrhea after hospitalization for more than 3 days, routine bacterial culture and examination for ova and parasites is generally not warranted because of the extremely low yield; however, in such patients, assessment for *C. difficile* infection is likely to be quite important.

The presence of inflammation, as suggested by bloody or mucoid stools or fecal leukocytes in the setting of severe or persistent diarrhea, warrants diagnostic stool studies. To increase diagnostic yield, bacterial cultures and examination of stool for ova and parasites should be done in sets of three. Routine bacterial stool cultures are intended to detect the most common community-acquired bacterial pathogens such as *Salmonella* species, *Shigella* species, and *C. jejuni*; various other techniques are required for detection of other pathogens. In patients with bloody diarrhea who are afebrile and non-toxic appearing, Shiga-like toxin-producing *E. coli* should be suspected. Sorbitol-MacConkey agar culture (SMAC) is useful for isolation of *E. coli* O157:H7, which is presently the most commonly detected Shiga-like toxin-producing strain of *E. coli*. Enzyme immunosorbent assay (EIA) of a single stool sample for Shiga-like toxin, rather than culture, is recommended by some experts because EIA will also detect strains of Shiga-like toxin-producing *E. coli* that are not of the O157:H7 serotype. In patients who have received antibiotics within the preceding 6–8 weeks, EIA testing for *C. difficile* toxins should be done. Blood cultures are indicated in the patient with apparent infectious diarrhea and marked systemic toxicity.

Parasitic infections are best diagnosed by visualization of the parasite or its ova on stool examination. In most cases of apparent viral gastroenteritis, testing for the etiologic agent is not warranted. However, in suspected outbreaks of norovirus, polymerase chain reaction (PCR) testing of stool can provide important epidemiological data.

## General Treatment Considerations

Appropriate treatment considerations for infectious diarrhea should include volume repletion, electrolyte replacement, and, if indicated, antimicrobial therapy. If oral rehydration is not possible, intravenous fluid therapy with isotonic fluid (i.e., normal saline or lactated Ringer's solution) is warranted. Vital signs, electrolyte levels, and renal function should be closely observed. Anti-motility agents should be avoided

because of their propensity to exacerbate symptoms and the potential for precipitating toxic dilation of the colon (toxic megacolon).

Consideration of therapy of diarrhea with antimicrobials should be carefully made. The benefits of therapy must be weighed against the risks of potentially harmful sequelae of antimicrobial use, which include adverse drug side effects, induction of antimicrobial resistance, and induction of antibiotic-associated *C. difficile* (Tables 5 and 6).

## Common Diarrheal Syndromes

Infectious diarrhea represents a broad array of clinical presentations that can be categorized as follows: food poisoning, viral gastroenteritis, diarrhea in the returning traveler, acute community acquired infectious diarrhea, nosocomial infectious diarrhea (primarily caused by *C. difficile*), and subacute or chronic diarrhea due to parasitic diseases. In this section, clinically important features of these categories of infectious diarrhea are presented.

### *Food Poisoning*

Although technically an intoxication rather than an infection, the clinical presentation of food poisoning is often that of an acute infectious diarrhea. The ingestion of food contaminated by pre-formed toxin may lead to the acute onset of gastroenteritis within 6–12 h (10). Enterotoxins produced by *Staphylococcus aureus*, *B. cereus*, and *C. perfringens* are the most common causes of toxin-mediated food poisoning. Distinguishing features include the rapid onset of illness, lack of fever, and the self-limited nature of the disease.

*S. aureus* food poisoning generally follows ingestion of foods with high protein content such as cream filled pastries, poultry, pre-cooked pre-packaged meats, and egg salads. The cause of disease is not the organism, per se, but a staphylococcal enterotoxin; in the elderly, mortality is increased (11). The organism thrives in temperatures between 68° and 99° F, whereas the heat stable enterotoxin of *S. aureus* is not destroyed by temperatures of 140° F or more; thus, illness may occur following what appears to be an adequate re-warming of foods. Onset of nausea, vomiting, and diarrhea usually occurs within 1–6 h of ingestion (10). Ingestion of the heat-resistant *B. cereus* toxin can result in two different syndromes: The first syndrome is a short-incubation emetic illness with the onset of symptoms occurring within 1–6 h after ingestion and is commonly associated with fried rice. The other is a long-incubation (8–16 h) diarrheal syndrome that follows ingestion of contaminated food, typically meat or vegetable dishes. *C. perfringens* food poisoning generally occurs after ingestion of contaminated meats and gravies and, in its presentation, is similar to the long-incubation diarrheal syndrome of *B. cereus*.

Diagnosis is difficult because it requires isolation of the organism from the suspected food source. The mainstay of therapy is supportive care.

### ***Viral Gastroenteritis***

In the elderly, norovirus and rotavirus are the most common causes of viral gastroenteritis (5). Features that may distinguish viral from bacterial gastroenteritis among the elderly include the sudden onset of nausea and vomiting; attack rates are higher among women. Supportive care, including treatment of dehydration, is the cornerstone of therapy.

Norovirus, previously known as Norwalk or Norwalk-like virus, is recognized as a major cause of nursing home outbreaks of viral gastroenteritis with a resultant increase in hospitalizations and mortality (12). In 2000, the CDC estimated that approximately 50% of the 220 outbreaks of foodborne illness reported from six selected states were due to norovirus (13). Outbreaks in hotels and on cruise ships have been attributed to contaminated shellfish, fruit snacks, raspberries, and other usually uncooked foods (12). Norovirus is readily spread. Although fecal–oral transmission and the contamination of food are the common modes of infection, vomitus is also capable of transmitting the disease. Sudden onset of diarrhea, vomiting, or both is a common presenting symptom in Norovirus infection; in older patients, diarrhea appears to be a more prominent symptom than vomiting; the presence of fever is variable. Symptoms typically last no longer than 2–3 days, although in one study, 40% of hospitalized patients 84 years of age or older were still symptomatic after 4 days (14). In other studies, longer duration of symptoms has been associated with age 65 years or greater (15).

Due to the characteristic presentation and self-limited nature of viral gastroenteritides, diagnostic testing is not generally required. However, during outbreaks of apparently infectious gastroenteritis, an etiologic diagnosis is of epidemiological importance. PCR testing of stool is the most useful diagnostic test; other diagnostic tests that have been used include electron microscopy, testing for viral antigen in stool, and serological tests (12). As with other viral causes of gastroenteritis, treatment is supportive. Implementation of infection control measures in institutional settings, as previously described, is of utmost importance in preventing transmission. Complications include aspiration pneumonia, renal failure, and hypokalemia.

### ***Diarrhea in the Returning Traveler***

A detailed discussion of traveler's diarrhea is beyond the scope of this review. As previously mentioned, knowledge of the geographically pertinent outbreaks and travel history is a valuable tool. Most often, diarrhea in the returning traveler

is self-limited. The presence of fever, passage of blood or mucus or both, and the presence of systemic toxicity are of concern and warrant an aggressive approach. Diagnostic evaluation, if necessary, should entail an approach similar to that discussed in section “Common Community-Acquired and Nosocomial Bacterial Causes of Infectious Diarrhea” on common bacterial causes of diarrhea.

Although some authorities recommend early self-treatment (i.e., institution of therapy at the first sign of gastroenteritis) with an oral fluoroquinolone while traveling outside the United States, as the major benefit to the patient is preserving time for sight-seeing, a not unreasonable goal; however, benefits are otherwise limited. Studies of self-treatment of “travelers” diarrhea have found a 1–3 day reduction in duration of symptoms with use of a fluoroquinolone such as ciprofloxacin (16). Viral gastroenteritis and food poisoning, of course will not be affected, and the risk of *C. difficile* infection would be increased by such practices.

## **Common Community-Acquired and Nosocomial Bacterial Causes of Infectious Diarrhea**

In 2006, the CDC’s FoodNet survey of the 17,252 laboratory confirmed cases of foodborne infections yielded the following five most common pathogens, four of which are bacteria: *Salmonella* species (6,655 cases), *C. jejuni* (5,712), *Shigella* species (2,736), *Cryptosporidium* species (859), and O157:H7 Shiga-like toxin-producing *E. coli* (17). Other less common pathogens including *Y. enterocolitica*, *Vibrio* species, and non-O157 Shiga-like toxin-producing *E. coli* (STEC) have been recognized.

### ***Shigella***

*Shigella* gastroenteritis is highly transmissible from person-to-person and commonly involves fever, malaise, abdominal cramping, diarrhea, and tenesmus (5). While hydration and supportive care are generally sufficient for management, limited data suggest that the risk of bacteremia is greater in patients with underlying diseases and those age 65 years and older (18). In some randomized control trials, antimicrobial therapy has shortened duration of diarrhea by 2–3 days, decreased duration of fever and tenesmus, and lowered the excretion of infectious organisms (19). Thus, it is reasonable that selected elderly patients receive antimicrobial therapy (5). Because of frequent resistance to trimethoprim–sulfamethoxazole, ampicillin, and nalidixic acid, a fluoroquinolone such as ciprofloxacin is the antimicrobials of choice (19). Being that *Shigella* is highly transmissible from person-to-person, aggressive infection control measures are indicated.



## ***Campylobacter***

Symptoms of *Campylobacter* infection are not distinguishable from other causes of bacterial gastroenteritis. Infection commonly occurs after ingestion of undercooked poultry or the re-use of inadequately decontaminated cooking surfaces or utensils during food preparation. Unfortunately, data are limited regarding efficacy of antimicrobial therapy in the elderly, and the benefits of antimicrobial therapy are thought to be limited. The utility of fluoroquinolones has been greatly hindered, due to their increased use in poultry farming and development of resistance (19). Macrolide antibiotics such as azithromycin possess activity against *C. jejuni* and may reduce carriage of the organism; symptomatic benefit occurs only if treatment is given within 4 days after onset of symptoms.

## ***Salmonella Gastroenteritis (Not Due to S. typhi or S. paratyphi)***

There are hundreds of species of *Salmonella* that may cause diarrhea. In the elderly and in nursing home residents, *Salmonella* infections have an appreciably higher mortality rate (5). Symptoms of *Salmonella* gastroenteritis generally include nausea and vomiting followed by abdominal cramping and diarrhea; the elderly are also more likely to develop bacteremia (20). For young otherwise healthy patients, in uncomplicated cases, antibiotics are not recommended because the clinical benefit is small and their use is associated with an increased rate of chronic carriage and relapse (19). However, patients at increased risk of complications such as bacteremia, which includes those greater than 50 years of age, are generally thought to warrant antimicrobial therapy.

## ***Salmonella typhi (Enteric Fever)***

Typhoid or enteric fever is a severe systemic and potentially fatal illness, usually due to ingestion of water or food contaminated by *S. typhi* or *S. paratyphi* (21). After an incubation period of 7–14 days, fever, systemic toxicity, and abdominal symptoms develop that may or may not be preceded by diarrhea; bacteremia is common. Other less common symptoms and signs may include bradycardia, mental status changes, hepatosplenomegaly, and rose spots—a maculopapular, salmon-colored truncal rash. Untreated infection occasionally leads to metastatic infection, including endocarditis, pericarditis, pneumonitis, and focal abscess formation. Infection of Peyer's patches in the distal small bowel or cecum may cause bowel wall necrosis and intestinal perforation. A chronic carrier state (gallbladder primarily) that can serve as a reservoir for infection of others is well-known. Diagnosis requires isolation of the organism from stool, blood, bone marrow, or other normally sterile sites. Due to the increasing resistance

of *S. typhi* to many antibiotics, ciprofloxacin or an equivalent fluoroquinolone should be used as first-line therapy.

## ***E. coli***

There are four major groups of diarrhea-causing *E. coli*: these are enteroinvasive *E. coli*, enterotoxigenic *E. coli*, enterohemorrhagic *E. coli*, and enteroadherent *E. coli*. An increasingly recognized cause of large outbreaks of infectious diarrhea in the United States is the Shiga-like toxin-producing enterohemorrhagic *E. coli* or STEC. This Shiga-like toxin is closely related to a toxin produced by *Shigella dysenteriae* and can cause bloody diarrhea, hemorrhagic colitis, and, in a small percentage of cases, hemolytic uremic syndrome (22). The most common strain of STEC is *E. coli* O157:H7; however, many other non-O157 strains of STEC can cause a similar syndrome.

A CDC review of recent outbreaks has implicated raw or undercooked beef, other meats, cheeses, spinach, onions, and person-to-person transmission as sources of infection (23). The clinical manifestations are varied, making for a challenging diagnosis. Bloody diarrhea in the setting of an outbreak should prompt further investigation. Fever and systemic toxicity are typically absent; this absence can be a helpful diagnostic clue in the patient with bloody diarrhea (24). Symptomatic infection generally resolves within a week; however, hemolytic uremic syndrome (HUS) can develop 2–14 days after the onset of diarrhea. Some data also suggest that the extremes of age are a risk factor for developing HUS. In an outbreak of elderly nursing home patients, 22% developed HUS (25). Other findings associated with the development of HUS include fever, bloody diarrhea, elevated leukocyte count and use of antimotility drugs (24). Although the mechanism by which HUS develops is not well understood, antibiotics are generally contraindicated because their use is associated with an increased risk for developing HUS (19). Therapy usually is supportive, and it is important that the clinician exclude STEC as the cause of infectious diarrhea prior to instituting antimicrobial therapy; an obvious exception is the patient with an apparent enteric infection and systemic toxicity. During a nursing home outbreak among elderly patients, the case fatality rate of *E. coli* O157:H7 was 35% (25). Etiologic diagnosis is also of great epidemiological value. *E. coli* O157:H7 can be recovered from feces using a specialized culture media, Sorbitol-MacConkey agar culture. Detection of the STEC toxin in stool samples can be done by EIA testing, if available; the advantage of the EIA test is that it will detect toxin produced by both O157:H7 and non-O157 strains.

## ***Antibiotic-Associated Diarrhea***

Diarrhea frequently occurs in association with antimicrobial use; approximately 5–25% of patients taking antimicrobials experience diarrhea (26); in most cases, the diarrhea is mild, is self limited, and is not due to *C. difficile*. Although

clindamycin, penicillins, and cephalosporins have been commonly implicated, other classes of antibiotics including fluoroquinolones, macrolides, and tetracyclines are also responsible. The cause of this nonspecific diarrhea related to antimicrobial use is thought to be due to increased levels of complex carbohydrates left undigested in the distal gut as a result of the antimicrobial suppression of the normal flora; the large molecules are thought to induce an osmotic diarrhea. In addition, specific antibiotics such as erythromycin or amoxicillin-clavulanate may stimulate bowel motility.

In the 1950s, 1960s, and 1970s, *S. aureus* was often implicated as the major pathogen in antibiotic-associated diarrhea (AAD). However, since the discovery of the role of *C. difficile* in the late 1970s, evidence to support an etiological role of *S. aureus* as a cause of AAD is meager. Currently, 10–20% of cases of AAD are attributable to *C. difficile* infection, while, as indicated above, the remainder are without an identifiable cause and resolve without specific therapy.

### ***Clostridium difficile* Infection**

Since 1978, *C. difficile* has been the only microbe that has been implicated in antibiotic-associated diarrhea and is the most common identifiable cause of bacterial diarrhea in the United States (27). Increasing prevalence among the elderly and recognition of a more severe form of infection has made *C. difficile* infection of particular concern; 2 to 3% of healthy adults are colonized. The rates of colonization among hospitalized adults range from 20 to 40% (28, 29). Most studies have identified three major risk factors for severe *C. difficile* infection: antibiotic exposure, advanced age, and hospitalization (27). A greater than 10-fold increase in infectious diarrhea has been observed in patients older than 60 years of age who were receiving antibiotics (30). Contributing to the heightened risk in the elderly are the following: residence in long-term care facilities, increase in hospitalizations, and antibiotic use. Diarrhea due to *C. difficile* is almost always associated with recent antibiotic use (27). Although clindamycin, ampicillin, and amoxicillin have been classically implicated, in the 1980s, cephalosporins became a prominent cause. At present, antimicrobial agents that are administered orally or that undergo hepatobiliary excretion will reach the colon in significant concentrations, altering the resistance of normal colon flora to colonization by *C. difficile* and thereby lead to *C. difficile* infection. Data linking gastric acid suppressants to an increased risk of CDI are conflicting.

*Clostridium difficile* is widely distributed in nature and its ability to form spores that can persist in the environment for extended periods is thought to explain the frequency of this infection. Recent studies suggest a widespread epidemic attributable to a new strain of *C. difficile* that has been referred to by various names (NAP1, BI, toxinotype III, and ribotype 027) (27). Canadian data from 1991 to 2003 has shown a 10-fold increase in the frequency of CDI, increased case fatality, and marked increase in incidence of recurrence amongst hospitalized patients aged

65 or older (31, 32); U.S. studies suggest a similar trend (27). A variety of potential explanations for the increase in incidence, morbidity, and mortality have been studied. These explanations include an increase in the production of *C. difficile* toxins A and B due to a deletion in the gene-regulating production of these toxins; production of a binary toxin by *C. difficile*; development of resistance to certain fluoroquinolones; and a number of potential breaches in infection control practices and policies. Diarrhea due to *C. difficile* is toxin mediated. Toxin A, the enterotoxin, is thought to be responsible for fluid secretion and inflammation. Toxin B is a cytotoxin that elicits direct cell damage. In addition to diarrhea, the patient may have abdominal cramps, high fever, marked leukocytosis, protein-losing enteropathy, and a nonspecific colitis; pseudomembranous colitis is characterized by detection of colonic plaques or of a pseudomembrane during endoscopy (27). The finding of colonic plaques, or pseudomembranes, is considered diagnostic for CDI but occurs in no more than 50% of cases and requires an invasive procedure for detection. Prominent complications of CDI include toxic megacolon, necessitating colectomy, bowel perforation and peritonitis, septic shock, and death.

Diagnosis of CDI can be challenging. Tissue culture assay for toxin B is the gold standard but is not generally available and requires at least 24–48 h to complete. Detection of toxins A and B by EIA is the most commonly used and widely available test—a single stool sample submitted for testing is sufficient. Unfortunately, the EIA test lacks sensitivity. A review of several studies places the range of sensitivity of the EIA at approximately 65–90% (relative to a positive tissue culture assay for toxin B in the presence of colonic plaques, or pseudomembranes at endoscopy) (27). A negative EIA for toxins A and B does not exclude the diagnosis, requiring that treatment decisions be individualized; a positive EIA test can be considered diagnostic.

Successful treatment of CDI is multi-faceted and, whenever possible, includes cessation of the offending antibiotic, hydration and electrolyte repletion, avoidance of anti-peristaltic agents, and use of antimicrobial therapy directed against *C. difficile*. The current mainstays of antimicrobial therapy are orally-administered metronidazole and orally-administered vancomycin; both are active against essentially all isolates of *C. difficile*. Although a number of antimicrobial agents are active against *C. difficile*, including several investigational agents, it does not appear likely that any of these agents will offer significant advantages over metronidazole and vancomycin.

Recently, it has been recognized that guidelines are needed to assist the clinician in choosing whether to treat with metronidazole or vancomycin. The concentration of metronidazole in the distal bowel after oral administration is relatively low and tends to decrease as diarrhea improves. This low concentration of metronidazole is due to efficient absorption in the proximal bowel; when diarrhea is waning, some experts believe that metronidazole levels in the colon may not be adequate for continual suppression of *C. difficile*. (33) The use of vancomycin has been limited due to high cost, a fear of increasing the prevalence of vancomycin-resistant *Enterococcus*, and induction of vancomycin-resistance in *S. aureus*. The initial decision regarding antibiotic therapy for CDI should include assessment of disease severity. A scoring system can be used to identify a patient's disease severity,

(Table 4). A severity score of two or less connotes mild disease (Table 4). In mild cases (and when clinically feasible), observation without specific therapy after discontinuation of the offending antimicrobial agent can be expected to lead to resolution of diarrhea in 80–90% of documented cases. If discontinuation of the offending agent is not possible, metronidazole can be administered orally (1.5–2.0 g/day in three to four divided doses for 7–10 days). A severity score of three or more (Table 4) indicates moderately severe to severe disease and warrants oral vancomycin therapy (125–250 mg 4 times a day for 7–10 days). For the patient with severe disease, consultation with a specialist may be warranted.

A significant therapeutic challenge for the clinician arises in the patient with diarrhea that is clinically thought to be due to *C. difficile* yet for whom the EIA test for toxin A and B is negative; because a falsely negative test is almost invariably negative on repeated testing, repeat testing has been shown to be of little benefit. In most laboratories, the only diagnostic test available for CDI is the toxin A/B EIA. Because of the relatively poor sensitivity of this test, the decision not to start or to stop treatment for CDI must be individualized. If the clinical situation strongly supports a diagnosis of CDI or there has been initial improvement with empirical treatment, it is usually prudent to complete a course of treatment, despite the negative EIA for *C. difficile* toxins. If a toxin B (cytotoxin) tissue culture assay can be obtained, the result is likely to clarify the situation; generally, however, the patient can be managed successfully without this test. The use of orally administered binding resins such as cholestyramine and of probiotics is of limited value and is usually not warranted.

Approximately 25% of patients with CDI treated with either metronidazole or vancomycin will have a relapse or recurrence of symptoms within days to weeks of completing therapy, despite having had a clear-cut initial response to treatment with resolution of diarrhea; relapses may be multiple. The initial relapse can be effectively

**Table 4** Clostridium difficile infection (CDI) Severity Scoring System<sup>a</sup>

Clinical finding	Point value
Fever (>38.0°C)	1
Ileus <sup>b</sup>	1
Systolic Blood Pressure <100 mm Hg <sup>c</sup>	1
Leukocytosis (in 1,000 cells/mm <sup>3</sup> )	
WBC 15–30	1
WBC >30	2
CT Scan Findings (thickened colonic wall, colonic dilatation, ascites)	
1 finding	1
≥2 findings	2

WBC white blood cell count, CT computed tomography; Adapted from (39)

<sup>a</sup>Severity score of 2 or less connotes mild disease that can be treated by discontinuation of the offending antimicrobial agent or administration of orally-administered metronidazole

Severity score of 3 or more indicates moderately severe to severe disease that warrants treatment with orally-administered vancomycin and consultation with a specialist

<sup>b</sup>Ileus diagnosed by clinical examination or plain abdominal radiographs

<sup>c</sup>Any single reading within 3 days of CDI diagnosis

treated with metronidazole for 10–14 days, if that agent was used to treat the first episode of CDI. Treatment of further relapses may require a prolonged vancomycin taper (see Table 6).

### ***Review of Principles of Antibiotic Use for Bacterial Causes of Infectious Diarrhea***

Although antimicrobial therapy for specific bacterial causes of diarrhea has been discussed, it is worth underscoring the principles of antibiotic prescribing for those infections. Use of antibiotics should be pathogen directed. Empirical use in moderate to severe disease must be directed towards the most likely causes of infectious diarrhea. In an era of increasing frequency and severity of infection with *C. difficile*, the initial approach should always include the detection of antibiotic exposure to antibiotics within 6–8 weeks of the onset of symptoms. When *C. difficile* is suspected, it is reasonable, while awaiting stool studies, to initiate therapy for mild to moderate disease with metronidazole. (see earlier discussion on CDI). Of equal importance, is cessation of the offending antibiotic, when clinically feasible, in an attempt to assist in the reconstitution of normal bowel flora. In cases of severe CDI or in disease requiring an intensive care unit admission or higher level of care, consideration should be given to initial therapy with oral vancomycin along with consultation with a subspecialist in gastroenterology or infectious diseases.

When history is not suggestive of CDI, (i.e., no recent antibiotic use) then other pathogens should be considered. Bloody diarrhea without fevers should raise suspicion for enterohemorrhagic *E. coli* or STEC. In mild cases without evidence of invasive disease, supportive care is the mainstay of therapy.

In severe cases of infectious community acquired or traveler's diarrhea, consideration should be given to possible bacteremia or sepsis due either to an enteric pathogen or to another infectious etiology. Use of empirical antimicrobial therapy in moderate to severe cases is reasonable and appropriate (2, 19). Pending stool studies and empirical antimicrobial therapy can be directed towards the major causes of infectious diarrhea in the community (Table 5). Initiating therapy with a fluoroquinolone such as ciprofloxacin (500 mg orally twice a day for 5–7 days) is adequate for most community-acquired pathogens in the elderly, including *Shigella* and *Salmonella* but not for *C. jejuni*. The high prevalence and increasing frequency of fluoroquinolone resistance by *C. jejuni* poses a challenge. A history of ingestion of undercooked poultry or use of unwashed cooking tools is suggestive of *C. jejuni* infection and can be very useful. If therapy is warranted, a macrolide such as orally-administered azithromycin would be the treatment of choice for *C. jejuni* enteritis; however, the utility of therapy is marginal. Although macrolides reduce the carriage of the organism, a reduction in diarrhea is noted only when medications are started within 4 days of the onset of symptoms (19). In general, there are very limited data regarding the efficacy of antimicrobials in the elderly with *C. jejuni* enteritis.

**Table 5** Initial approach to infectious diarrhea

Clinical situation	Comments
Suspicion for mild to severe CDI (IV or PO antimicrobial use within last 6–8 weeks)	Assess Disease Severity (Table 4) See Table 6
Mild to moderate community acquired disease <sup>a</sup>	Supportive therapy Antimicrobial agent not indicated Avoid anti-peristaltic agents Enforce infection control measures (i.e., hand-washing and isolation of patient if indicated)
Severe community acquired disease <sup>a</sup>	Fluoroquinolones with good activity against <i>Salmonella</i> spp. and <i>Shigella</i> spp. (activity against other pathogens is variable) Alternate: 3rd generation cephalosporin

CDI *Clostridium difficile* infection, IV intravenous; PO oral

<sup>a</sup>No suspicion for *C. difficile*

## Chronic Diarrhea Due to Parasitic Infections

### *Cryptosporidium parvum*

*Cryptosporidium* is the most commonly isolated parasitic cause of foodborne illness in the United States and is the fourth most commonly identified pathogen in foodborne illness (17). The self-limited nature of the disease in immunocompetent patients and the difficulty in identification of the organism, likely leads to an under-reporting of the disease. The most likely source of *Cryptosporidium*, a water-borne parasite, is swimming pools or unfiltered water supplies. Common symptoms of cryptosporidiosis include abdominal pain and diarrhea in most and fever in approximately 50% of cases (34). In a series of 68 otherwise healthy patients, all spontaneously recovered with a mean symptom duration of approximately 12 days (range: 2–26 days). Stool samples are necessary for diagnosis, and it is essential to alert the testing laboratory of the suspicion for cryptosporidial infection. *Cryptosporidium* usually will not be detected during routine examination of the stool for parasites and their ova; however, cysts may be identified by a modified acid-fast stain. Enzyme-linked immunosorbent assays (ELISA) are also available. Although there are no reliably effective therapies, the disease is self-limited in otherwise healthy individuals. However, some may be asymptomatic cyst shedders for weeks to months before resolution. In immunosuppressed individuals, *Cryptosporidium* may cause protracted, potentially lethal diarrhea.

### *Giardia lamblia*

Between 1998 and 2002, the number of cases of giardiasis has decreased in the United States (35). The major mode of transmission is via ingestion of water-borne

cysts followed by a 1–2 week incubation period. The clinical presentations of giardiasis are varied but usually include prolonged diarrhea. An acute syndrome with diarrhea and weight loss of several weeks' duration can occur and is often self-limited (36). Rarely, acute infections are associated with urticaria and reactive arthritis. In the chronic diarrhea syndrome upper gastrointestinal symptoms are infrequent, and clinical evidence of malabsorption and weight loss is common. Loose, foul-smelling stools are often associated with cramping and flatulence. Complications of chronic infection can include inflammatory disease of the small bowel with villous atrophy; fecal leukocytes, mucous, and blood are absent. An asymptomatic carrier state is not uncommon. Definitive diagnosis can be made by identification of the cysts or trophozoites in the stool or by detection of *Giardia* antigen in the stool by EIA. Treatment is metronidazole (Table 6).

**Table 6** Therapy for specific pathogens

Pathogen	Treatment
<i>Salmonella</i> (not <i>S. typhi</i> or <i>S. paratyphi</i> ) <sup>a</sup>	Ciprofloxacin 500 mg PO BID × 5–7 days
<i>Salmonella typhi</i> (or <i>S. paratyphi</i> ) <sup>a</sup>	Ciprofloxacin 7.5 mg/kg PO BID × 5–7 days (uncomplicated typhoid fever) OR × 10–14 days (complicated typhoid fever)
<i>Shigella</i> species <sup>a</sup>	Supportive therapy
<i>Campylobacter jejuni</i> <sup>a</sup>	Azithromycin 500 mg PO QD × 3 days (Fluoroquinolones NOT effective)
<i>Vibrio cholerae</i> O1 or O139 <sup>b</sup>	Aggressive fluid and electrolyte replacement Doxycycline 300 mg PO × 1
<i>Clostridium difficile</i>	<i>Mild disease:</i> Cessation of current antibiotics, when feasible, and observation <i>or</i> metronidazole 500 mg PO TID (×10–14 days) while awaiting stool studies <i>Moderate to severe disease:</i> Vancomycin 125–250 mg PO QID while awaiting stool studies; if bowel hypomotility or atony, consider addition of metronidazole 500 mg IV TID <i>Second relapse/recurrence of CDI:</i> Vancomycin 125 mg qid × 2 weeks, then Vancomycin 125 mg bid × 1 week, then Vancomycin 125 mg qd × week, then Vancomycin 125 mg q2–3 days for 2–8 weeks
<i>Giardia lamblia</i>	Metronidazole 250–750 mg PO TID × 7–10 days
<i>Entamoeba histolytica</i>	Metronidazole 750 mg PO TID × 5–10 days, followed by a lumincidal agent <sup>c</sup> : Iodoquinol 650 mg PO TID × 20 days, or Paromomycin 500 mg PO TID × 7 days

PO oral, QD once day, BID 2 times/day, TID 3 times/day, QID 4 times/day, CDI *C. difficile* infection

<sup>a</sup>When stool cultures are reported as positive for *Salmonella*, *Shigella*, or *Campylobacter*, it may be reasonable to treat with an antimicrobial agent if patient has not improved at the time culture results become available; however, with the exception of *S. typhi* and *S. paratyphi*, if the patient's symptoms have resolved or improved substantially when culture results become available, antibiotics would usually not be indicated

<sup>b</sup>Cultures for *V. cholerae* require special media

<sup>c</sup>A lumincidal agent necessary for eradication of cysts and prevention of recurrence



## *Entamoeba Histolytica*

The most common population of patients affected by *E. histolytica* is immigrants. Similar to *Cryptosporidium* and *Giardia*, *E. histolytica* is a food or water-borne pathogen (37). Presentations are often subacute (generally over 1–3 weeks) with symptoms ranging from mild diarrhea to severe dysentery and weight loss (37, 38). Generally, stools are either grossly bloody in the case of dysentery or are positive for occult blood in less severe cases; fecal leukocytes are absent. Complications, although infrequent, include toxic megacolon and amebic liver abscesses. Diagnosis can be made by identification of the parasite in the stool. Serologic assays are available but lack specificity. Treatment is with metronidazole to kill trophozoites in tissue, followed by a luminal agent such as iodoquinol or paromomycin, to eradicate cysts (Table 6).

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# Urinary Tract Infection

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## Key Points

- Urinary infection is the most common bacterial infection that occurs in older populations.
- Urinary infection in older men and women is usually asymptomatic and accompanied by pyuria. Treatment of asymptomatic bacteriuria is not indicated.
- Long-term care facility residents with chronic indwelling catheters are uniformly bacteriuric secondary to biofilm formation on the catheter.
- A positive urine culture is not sufficient for diagnosis of symptomatic urinary infection, but a negative urine culture, collected prior to institution of antimicrobial therapy, will exclude infection.
- For residents of long-term care facilities without indwelling catheters, a diagnosis of symptomatic urinary tract infection requires localizing genitourinary symptoms or signs.

## Epidemiology and Clinical Relevance

Urinary infection is an important clinical problem. For elderly populations it occurs along the full continuum from the ambulant, well elderly in the community to the highly functional disabled long-term care facility resident. Management approaches may vary for different elderly populations. In addition, there are unique considerations for urinary infection in subjects with long-term indwelling catheters.

The site of infection within the genitourinary tract may be the bladder, kidney, and, for men, the prostate. The kidney, ureters, bladder, and proximal urethra are

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normally sterile. Urinary tract infection is the presence of significant numbers of bacteria within the genitourinary tract and may be asymptomatic or symptomatic. Bacteriuria simply means bacteria in the urine. This term is usually used in the context of “significant bacteriuria” and is interchangeable with the term urinary tract infection. While the term “bladder colonization” is sometimes used rather than asymptomatic urinary infection, this term, in elderly populations, has no clearly defined clinical meaning. In addition, the older individual with bacteriuria usually has evidence for a host response within the genitourinary tract. Thus, the term “colonization” is not used here, and the term “bacteriuria” is used interchangeably with asymptomatic urinary tract infection.

### ***Prevalence and Incidence***

In elderly populations, urinary tract infection is the most common bacterial infection. Healthy, young, sexually active women have a prevalence of positive urine cultures of 2–5%, and this increases to 5–10% for women aged 65 years and older (1). A positive urine culture is uncommon in younger men, but the prevalence for men aged 65 years and older is 5% or higher. Residents of long-term care facilities have an extraordinary prevalence of bacteriuria: 25–50% for women and 15–40% for men. The prevalence increases with increasing levels of functional disability in the institutionalized population.

There is also a high incidence of urinary infection in the elderly population. A Seattle cohort of post-menopausal women aged 55–75 years experienced 7 symptomatic infections per 100 patient years (2). Mims and colleagues (3) reported a frequency of symptomatic urinary infection of 0.17 per 1,000 days for elderly ambulatory male outpatients at a veteran’s hospital. In these men, 10% of 209 who were initially not bacteriuric developed bacteriuria during a mean follow-up of 2.8 years. However, 76% of these elderly ambulatory men cleared their asymptomatic bacteriuria spontaneously. Hospitalization rates for pyelonephritis have been reported to be 10–15 per 10,000 for men or women over age 70 years in a Canadian province (4) and 13.5–23.3 per 10,000 and 6.3–12.9 per 10,000, respectively, for women and men over 60 years in the United States (5).

In institutionalized, elderly populations, the rate of acquisition of bacteriuria is also high. For male residents of one nursing home, an incidence of urinary infection of 45 per 100 patient years was reported, with 10% of nonbacteriuric residents becoming bacteriuric every 3 months (6). Women in a nursing home initially identified as bacteriuric and not treated with antibiotics had 87 new infections per 100 patient years (7). The high frequency of urinary infection in institutionalized populations is also described by the “turnover” of bacteriuria (8). From 10 to 20% of initially nonbacteriuric institutionalized men or women will have become bacteriuric at 6–12 months follow-up, and 25–30% of bacteriuric residents will become nonbacteriuric in the same time period. Thus, in these populations, asymptomatic urinary infection is common and dynamic.

Elderly ambulatory women residents of a geriatric apartment had an incidence of symptomatic infection of 0.9 per 1,000 days (9). The incidence of symptomatic urinary infection for the institutionalized population has been reported to range from 1.0 to 2.4 per 1,000 resident days (8) or as low as 0.11–0.15 symptomatic infections per bacteriuric resident year when more restrictive definitions are used (6, 7). In a prospective study in two large nursing homes, the incidence of urinary infection with fever was reported to be 0.49–1.04 per 10,000 resident days (10).

### ***Pathogenesis***

The reasons for the very high frequency of urinary infection in elderly, ambulatory populations are multiple and are not yet fully characterized. Changes in the immune system due to aging have not been reported to be associated with an increased risk of urinary infection. For men, prostate hypertrophy resulting in urinary retention and turbulent urethral urine flow is the most important contributing factor. When bacterial prostatitis occurs, recurrent urinary infection from a prostate source may occur because of limited diffusion of antimicrobials into the prostate as well as the frequent presence of infected prostate stones in older men. Other genitourinary abnormalities that promote infection and occur with increased frequency in older men or women include urethral or ureteric strictures due to fibrosis or tumors and renal or bladder stones.

Women who experience acute, uncomplicated urinary infection at a younger age remain at risk for this clinical syndrome when they are postmenopausal. The strongest and most consistent association of recurrent urinary infection in postmenopausal women is a prior history of recurrent urinary tract infection beginning in childhood or young adult years (2). Unlike younger women, sexual activity is not a risk factor for infection in older women. In addition, older women are more likely to have urologic abnormalities such as cystoceles and increased post-void residual volumes that increase the risk of complicated urinary tract infection (11). Incontinence has been repeatedly associated with urinary infection in older women, but both incontinence and urinary infection are concomitants of impaired bladder function rather than incontinence being a cause of infection.

In postmenopausal women, loss of the estrogen effect on the genitourinary mucosa has been suggested to be an important contributor to urinary infection. Consistent changes in the normal vaginal flora attributed to the aging-associated decline in estrogen are observed in postmenopausal women (12). Lactobacilli which maintain an acid pH are less common and replaced by organisms such as *Escherichia coli* and *Enterococcus* spp. However, in a prospective study, no association between vaginal flora changes and recurrent urinary tract infection was observed (2).

For institutionalized men and women, the prevalence of bacteriuria is highest in the most functionally impaired; these individuals usually have incontinence of bladder or bowel, are confused or demented, and have impaired mobility (8, 13). Comorbid diseases that necessitate institutional care, such as Alzheimer's disease, Parkinson's

disease, or cerebrovascular accidents are usually accompanied by impaired bladder function. There is compromised bladder emptying and ureteric reflux may occur, contributing to the high frequency of infection in these residents. For men, external condom catheters are frequently used to manage incontinence. These devices are associated with a twofold increase in frequency of infection increased in section when there is twisting or obstruction of the drainage tube at increased risk.

## Microbiology

For elderly women residents in the community, *Escherichia coli* is the single most common infecting organism, although the proportion of infections from which this organism is isolated is lower than observed in younger women (Table 1). Other organisms isolated include *Klebsiella* spp., *Proteus* spp., and group B streptococcus (*Streptococcus agalactiae*). Coagulase-negative staphylococci are frequently isolated from ambulatory elderly men but are seldom associated with symptomatic infection (3). When men present with symptomatic infection, *E. coli* and *Proteus mirabilis* are the most frequent organisms. *Enterococcus* spp. is also a common infecting organism.

*E. coli* remains the most frequent organism isolated from institutionalized women but occurs in only 50–60% of episodes (7). *P. mirabilis* and other Enterobacteriaceae are isolated with increased frequency in elderly women. For men, *P. mirabilis* is isolated more frequently than *E. coli* (6). The intensity of antimicrobial use in long-term care facilities, together with facilitated transfer of organisms between patients in the institutional setting, promotes infection with organisms characterized by increased antimicrobial resistance. *Providencia stuartii*, *Pseudomonas aeruginosa*, and Enterobacteriaceae such as *Klebsiella* spp., *Enterobacter* spp., *Serratia* spp., and *Citrobacter* spp., are common in urinary infection in these settings and may be resistant to multiple antimicrobials.

Isolation of more than one organism from urine culture should not be assumed to be contamination. Polymicrobial bacteriuria is common in the bacteriuric

**Table 1** Bacteriology of urinary infection in asymptomatic elderly populations

Organisms	Percent of infections with organisms isolated			
	Community		Institution	
	Men	Women	Men	Women
<i>Escherichia coli</i>	19	68	11	47
<i>Proteus mirabilis</i>	5	1	30	27
<i>Klebsiella pneumoniae</i>	5	10	6	7
<i>Providencia stuartii</i>			16	7
<i>Pseudomonas aeruginosa</i>	5		19	5
Other gram-negative bacteria	2		7	6
<i>Enterococcus</i> spp.	25	5	5	6
<i>Streptococcus agalactiae</i>	39	10	–	1
Coagulase-negative staphylococci		6	2	–
Other gram-positive bacteria			3	–

institutionalized elderly. From 15 to 25% of women and 10 to 15% of men with bacteriuria may have more than one organism isolated (6, 7). Men with incontinence that are managed by external condom catheter drainage have an increased frequency of polymicrobial bacteriuria.

### ***Morbidity and Mortality***

In elderly populations, urinary infection contributes to morbidity, but the burden is limited relative to the very high frequency of infection. Short-term morbidity is usually symptomatic urinary infection presenting along a spectrum of lower tract irritative symptoms (acute cystitis), through acute pyelonephritis, bacteremia and, rarely, death. Local infectious complications may include epididymitis and prostatitis in men, or bladder and renal stone formation associated with urease-producing organisms such as *P. mirabilis* or *P. stuartii*. An additional problem for institutionalized populations is the emergence of organisms of increased antimicrobial resistance following repeated antimicrobial exposure. Residents with asymptomatic bacteriuria provide a substantial reservoir for such resistant organisms (8).

In elderly populations, urinary infection is the most frequent cause of community-acquired bacteremia. The majority of elderly patients with bacteremia from a urinary source, however, will have abnormalities of the genitourinary system such as acute retention, tumor, or an indwelling catheter. Urinary infection is also the most frequent source of bacteremia in long-term care populations and a common precipitating cause for acute care hospitalization of long-term care residents. Occasionally, urinary infection presents a sepsis syndrome with and death from gram-negative septicemia may occur; however, this is uncommon relative to the very high frequency of urinary infection. The most serious presentations of urinary infection usually occur in individuals with significant structural genitourinary abnormalities, including long-term indwelling catheters. Death of residents in long-term care facilities is only rarely directly attributable to urinary infection.

Bacteriuria is frequently persistent or recurrent over many years. There is no evidence that prolonged bacteriuria is associated with poorer long-term clinical outcomes compared with institutionalized elderly residents without bacteriuria. Specifically, persistent bacteriuria is not associated with an increased risk of hypertension or chronic renal failure. In addition, despite a very high prevalence of infection with urease-producing organisms in many long-term care facility residents, complications secondary to urolithiasis are infrequent.

In both Greece and Finland, early studies reported an association of asymptomatic bacteriuria with decreased survival in elderly populations. These studies did not adjust for differences in functional or medical status between bacteriuric and nonbacteriuric subjects. Subsequent studies from community populations in Finland and Sweden (14) and in institutionalized populations in the United States (15) and Canada (13) reported no association between asymptomatic bacteriuria and



survival. In fact, a survival difference between bacteriuric and nonbacteriuric elderly subjects might be anticipated, as the bacteriuric group has poorer functional status.

### ***Long-Term Indwelling Urethral Catheters***

From 5 to 10% of residents in long-term care facilities have bladder emptying managed through the use of a long-term indwelling urethral catheter (16). The most frequent indications for catheter use are urinary retention in men, urinary incontinence in women, and to assist with pressure ulcer healing. Chronic indwelling urethral catheters are uniformly coated on both external and internal surfaces with a bacterial biofilm (17). The biofilm is composed of a glycopeptide matrix produced by the organisms that initially adhere to the device then grow within the biofilm. Constituents from the urine are also incorporated into the biofilm, including calcium, magnesium and Tamm–Horsfall protein. The biofilm provides an environment within which organisms persist and are relatively protected from both antimicrobials and host defenses. Individuals with chronic indwelling catheters are always bacteriuric, with usually 2–5 organisms at any time. Urease-producing organisms such as *P. mirabilis* and *P. stuartii* have increased biofilm production. This may be associated with an increased likelihood of catheter obstruction due to biofilm formation along the interior surface of the catheter when these organisms are present.

Residents managed with long-term urethral catheters have a higher incidence of urinary infection as compared to bacteriuric residents without indwelling catheters (10, 16). The usual clinical presentation of urinary infection is with systemic manifestations such as fever or bacteremia. Local complications of urinary infection may also occur; these include urethritis, urethral fistula, epididymitis, prostatitis and prostate abscess, and scrotal abscess. Bladder stones may develop when urease-producing organisms are present. At autopsy, histologic evidence for acute pyelonephritis is identified in a higher proportion of nursing home residents with chronic indwelling catheters as compared with those with asymptomatic bacteriuria without chronic indwelling catheters (16). Thus, bacteriuria with a chronic indwelling catheter in situ is associated with increased morbidity compared with asymptomatic bacteriuria in noncatheterized elderly subjects. Residents of long-term care facilities with chronic indwelling catheters have also been reported to have decreased survival (18), but this observation is unlikely directly attributable to the catheter or catheter-acquired bacteriuria, as the population with an indwelling catheter has greater medical and functional impairment.

### **Clinical Manifestations**

In elderly populations, urinary infection is usually asymptomatic (19). That is, the urine culture is positive, but there are no acute genitourinary or systemic symptoms attributable to the infection. When symptomatic infection does occur, it may

present as acute lower tract irritative symptoms such as frequency, dysuria, urgency, or suprapubic discomfort and, particularly in elderly women, acute deterioration of continence status. Infection may also present with systemic manifestations such as pyelonephritis with fever and costovertebral angle pain and tenderness, or fever with hematuria without other localizing findings. Fever with urinary obstruction or following trauma to a chronic indwelling catheter are additional presentations of urinary infection. Bacteremic infection is most likely to occur in the setting of ureteral or urethral obstruction or mucosal trauma.

A clinical diagnosis of acute symptomatic urinary infection in elderly populations is often not straightforward (see Table 2) (10, 19). It is most problematic in the institutionalized population who have chronic symptoms attributable to comorbid diseases and difficulties in communication which interfere with clinical assessment. Chronic genitourinary symptoms such as chronic incontinence and nocturia are not attributable to urinary infection, although many elderly individuals with these symptoms have a positive urine culture (19, 20). Where a patient has a fever and localizing genitourinary symptoms or signs such as acute retention, catheter obstruction, hematuria, or costovertebral angle tenderness, a clinical diagnosis of urinary infection may be made with a degree of certainty. For the non-catheterized elderly subject with fever and without localizing genitourinary findings, urinary tract infection is unlikely (10). A positive urine culture is present in 25–50% of the institutionalized population at any time, so residents with symptoms from any cause have a high probability of a positive urine culture. Only about 10% of episodes of fever without localizing genitourinary symptoms in bacteriuric residents without indwelling catheters have a urinary source (10); however, in residents with a chronic indwelling urethral catheter, as many as one-third of such episodes will be from a urinary source.

In institutionalized populations, there are other dilemmas in the diagnosis of symptomatic urinary infection. In residents of long-term care facilities, “foul-smelling urine” is frequently attributed to urinary infection and inappropriately, considered

**Table 2** Clinical presentations of urinary tract infection in elderly bacteriuric subjects

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**Probable urinary infection**

Acute onset or deterioration in lower tract symptoms: frequency, dysuria, suprapubic pain, urgency

Fever with:

Costovertebral pain/tenderness

Hematuria

Acute retention

Catheter obstruction

**Possible urinary infection**

Acute deterioration in continence status

Fever without localizing findings:

Indwelling catheter (30% probability)

No indwelling catheter (10% probability)

**Unlikely symptomatic urinary infection**

Chronic incontinence, or other chronic genitourinary symptoms

Clinical deterioration without localizing genitourinary findings in persons without chronic indwelling catheters

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an indication for antimicrobial therapy. Urinary infection may be associated with an unpleasant odor, likely secondary to polyamine production by bacteria in the urine. However, not all subjects with bacteriuria will have an unpleasant odor to the urine, and not all individuals with an unpleasant urine odor have a positive urine culture (19). Dehydration may also contribute to unpleasant odor. Approaches such as hydration and improved continence management should be considered instead of antimicrobial therapy.

Another problematic clinical scenario is the elderly subject who has deteriorated clinically without localizing findings. Again, because of the high frequency of asymptomatic bacteriuria in this population, many of these individuals will have positive urine cultures. There are, however, no clinical studies that support a diagnosis of symptomatic urinary infection with this presentation. In this situation, the appropriate management is likely observation and reassessment rather than initiating antimicrobial therapy. Elderly subjects with fever and acute confusional states need prompt clinical evaluation, as this presentation may be consistent with sepsis. Urinary infection may be a source, but other diagnoses such as pneumonia are more likely.

## **Diagnostic Tests**

### ***Urine Culture***

A positive urine culture is necessary for the microbiologic diagnosis of urinary infection. While a positive urine culture is not sufficient to diagnose symptomatic infection, a negative urine culture will effectively exclude urinary tract infection as a diagnostic consideration. If symptomatic urinary infection is considered, a urine specimen is essential to identify the infecting organism and to obtain antimicrobial susceptibilities for optimal antimicrobial therapy. The urine specimen must be collected prior to the institution of antimicrobial therapy, as the urine culture becomes negative rapidly once antimicrobials are initiated.

An appropriate method for urine specimen collection that minimizes bacterial contamination must be used. For symptomatic men, a single clean-catch urine specimen is adequate and can usually be obtained. When voiding is managed with external condom catheters, a urine specimen may be collected immediately, postvoiding using a freshly applied condom and leg bag. A clean-catch specimen is preferred for women; however, it may not be possible to obtain a voided urine specimen from the most highly functionally impaired institutionalized women. When women cannot cooperate to obtain a voided specimen, and a urine specimen is indicated for assistance with clinical management, the specimen should be obtained by in-and-out urethral catheterization. Urine collection using a bedpan or pedibag is subject to substantial contamination with periurethral or vaginal flora. Diagnostic criteria for urinary infection have not been validated for these collection methods, and they should be discouraged.

A urine specimen obtained from the urinary catheter of residents with long-term indwelling catheters will sample the bacterial flora of the biofilm on the interior surface of the catheter and is not representative of bladder microbiology. Subjects with chronic indwelling catheters should have the catheter changed and a specimen obtained from the freshly inserted catheter, which samples bladder urine, prior to instituting antimicrobial therapy (21).

A urine culture growing  $\geq 10^5$  colony-forming units (CFU/mL) of one or more organisms on two consecutive specimens is required to diagnose asymptomatic urinary infection. A single urine culture with  $\geq 10^5$  CFU/mL is adequate for bacteriologic diagnosis in subjects with acute symptoms referable to the genitourinary tract. When the clinical presentation is consistent with acute pyelonephritis,  $\geq 10^4$  CFU/mL is the appropriate quantitative criteria. Quantitative counts of Enterobacteriaceae of  $< 10^5$  CFU/mL are isolated in 30% of episodes from younger women presenting with acute cystitis; whether this is similar for postmenopausal women with acute cystitis has not been studied. However, for healthy, non-institutionalized, older women the lower quantitative count of organisms may be appropriate for microbiologic confirmation of infection.

Lower quantitative counts of organisms may occur with *Candida albicans* infection. Patients with renal failure or those receiving diuretics with dilute urine may also have lower quantitative bacterial counts. Some uncommon infecting organisms such as *Ureaplasma urealyticum* or *Haemophilus influenzae* are not isolated using routine culture methods, and urine cultures may be negative, unless special cultures are requested. In the presence of complete obstruction to urinary drainage and infection proximal to the obstruction, for instance, ureteric obstruction due to a stone, stricture, or tumor, the voided urine culture may be negative, and a percutaneous aspirate from the proximal infected site is necessary to identify the infecting organisms.

## ***Pyuria***

Pyuria, the presence of excess leukocytes in the urine, is usually identified by routine urinalysis or by leukocyte esterase dipstick. It is virtually a universal finding in patients with symptomatic urinary infection. However, about 90% of elderly subjects with asymptomatic bacteriuria also have pyuria. The presence of pyuria, then, cannot differentiate asymptomatic from symptomatic infection (1). There is no evidence that the degree of pyuria is associated with adverse short- or long-term outcomes (22). Urease-producing organisms such as *P. mirabilis* or *P. stuartii* create an alkaline urine, and rapid disintegration of leukocytes at the higher pH may lead to false-negative tests for pyuria. Conversely, about 30% of residents of nursing homes with negative urine cultures also have pyuria. Thus, pyuria alone is not a diagnostic test for urinary infection and cannot replace urine culture. In addition, as pyuria does not differentiate symptomatic from asymptomatic infection, the presence or absence of pyuria in an individual with a positive urine culture does not determine whether or not antimicrobial therapy is indicated. However, a negative

diagnostic test for pyuria has a high negative predictive value and is a useful screening test to exclude urinary infection.

### ***Other Investigations***

Bacteremia occurs in some episodes of symptomatic urinary infection in older persons. These patients often have obstruction or trauma to the genitourinary tract. Blood cultures should be requested for patients presenting with a high fever, hypothermia, or hemodynamic instability.

A number of other inflammatory markers are present with urinary infection but have not been shown to have diagnostic or prognostic utility. Virtually all of these mediators are nonspecific indicators of infection at any site and not specific to urinary infection. Patients with significant systemic manifestations such as fever have an elevated C-reactive protein and elevated urine antibodies; interleukins and other cytokines or chemokines are also present. The elevated levels decline or disappear following effective treatment. However, urinary cytokines are also increased in a substantial proportion of subjects with asymptomatic bacteriuria, some of whom also have elevated urinary and systemic antibodies to the infecting organisms.

## **Treatment**

### ***Asymptomatic Infection***

Asymptomatic urinary infection in elderly populations should not be treated. Prospective, randomized, comparative trials of therapy compared with that of no therapy for the treatment of asymptomatic infection in institutionalized men or women have consistently failed to document improvements in morbidity or mortality with treatment (1, 6, 7, 15). For long-term care residents with chronic incontinence and bacteriuria, antimicrobial treatment of urinary infection does not improve continence (20). Attempts to treat asymptomatic infection with antimicrobial therapy are ineffective and, in fact, harmful due to increased adverse effects from medication, emergence of resistant organisms, and increased cost (7). Thus, the evidence is consistent that there are no benefits and that there are some adverse effects with treatment of asymptomatic bacteriuria. The presence of pyuria with bacteriuria is not an indication for antimicrobial therapy, as pyuria does not differentiate symptomatic from asymptomatic infection. It follows, then, that elderly asymptomatic subjects should not be screened for the presence of pyuria or bacteriuria, as there is no indication for treatment even if infection is identified (1).

Treatment of asymptomatic bacteriuria is recommended for individuals prior to invasive genitourinary procedures associated with mucosal trauma such as

transurethral resection of the prostate or cystoscopy in men (1). Following such procedures, there is a very high frequency of bacteremia and sepsis. Urine cultures to identify bacteriuria should be obtained and, if infection is present, antimicrobial therapy selected based on the organisms isolated. The antimicrobial should be started immediately prior to the surgical procedure. Antimicrobial therapy is given for prophylaxis to prevent urosepsis rather than for treatment of asymptomatic bacteriuria.

### ***Symptomatic Infection***

Symptomatic infection should, of course, be treated. The goal of therapy is to ameliorate symptoms not to sterilize the urine. Antimicrobial treatment is selected on the basis of the organism(s) isolated from the urine and the antimicrobial susceptibilities. Where the patient is sufficiently ill that empirical antimicrobial therapy must be given before urine culture results are available, a broad-spectrum antimicrobial agent effective against gram-negative organisms and enterococci is most appropriate. Oral therapy is usually adequate, but parenteral therapy is necessary where there are concerns about severity of illness, patient tolerance, drug absorption, or antimicrobial resistance. Parenteral therapy is usually changed to oral therapy once the patient is clinically stable and the results of pretherapy urine cultures are available, usually after the initial 2–4 days of treatment.

A problematic clinical issue is when to consider instituting antimicrobial therapy for presumed urinary tract infection in the bacteriuric subject with nonlocalizing symptoms. As previously discussed, unless an indwelling urethral catheter is in place, urinary infection is an unlikely source of clinical deterioration in the absence of localizing genitourinary symptoms. This question is addressed in a consensus document developed specifically to provide recommendations for the initiation of antimicrobial therapy in long-term care facilities (23). For the resident without an indwelling urethral catheter, empirical treatment is recommended with either acute onset of dysuria alone or when fever ( $>37.9^{\circ}\text{C}$ ) is documented together with one or more of the following: new or worsening urgency, frequency, suprapubic pain, gross hematuria, costovertebral angle tenderness, or urinary incontinence. For the resident with a chronic indwelling catheter, empirical therapy should be initiated for urinary infection when there is any one of the following: fever  $>37.9^{\circ}\text{C}$ , new costovertebral angle tenderness, rigors, or new onset delirium.

### ***Antimicrobial Selection***

Many antimicrobials are effective for the treatment of urinary infection in the elderly. Few studies, however, have specifically addressed the comparative efficacy of antimicrobial regimens to allow an informed choice based on the balance of

efficacy and adverse effects. Recommendations for antimicrobial selection in elderly populations are primarily based on studies performed in younger populations and frequently in clinical settings that are not relevant for the elderly. In addition, the local prevalence of antimicrobial resistance will direct decisions for empirical therapy in a given facility.

A list of antimicrobials that may be used for oral or parenteral therapy are provided in Table 3. Initial empirical oral therapy with trimethoprim/sulfamethoxazole (TMP/SMX) is usually recommended. If there is a possibility of TMP/SMX-resistant organisms, a fluoroquinolone may be the best alternate, although nitrofurantoin may also be considered for presumed lower tract infection with organisms other than *K. pneumoniae*, *P. mirabilis* or *P. aeruginosa*. Other antimicrobials may be appropriate based on patient tolerance or anticipated susceptibility of the organism. An aminoglycoside with or without ampicillin remains an effective empirical parenteral therapy. Although there are concerns about aminoglycoside nephrotoxicity, the expectation is that therapy will be reassessed at 48–72 h when culture results are available, and the antimicrobial therapy will be modified based on this information. Thus, the duration of empirical therapy with the aminoglycoside is minimized, and there is little risk of toxicity. In patients with renal failure, an aminoglycoside is not appropriate for initial empirical therapy, and an extended-spectrum cephalosporin or fluoroquinolone is recommended.

### ***Duration of Therapy***

Older women treated for urinary infection have a lower cure rate with any duration of therapy as compared with younger women. Previous recommendations suggested that postmenopausal women should be uniformly treated with longer courses of therapy for acute cystitis and short-course therapy of 3 days, which was the recommended standard for younger women and was not appropriate. However, a prospective randomized placebo controlled study in postmenopausal women of mean age 79 years, and without known urologic abnormalities, reported similar outcomes with 3 or 7 days of ciprofloxacin, and significantly fewer adverse drug effects with the 3-day regimen (24). Thus, for lower tract infection, a 3-day course of therapy is appropriate when a fluoroquinolone or TMP/SMX is prescribed. If nitrofurantoin or a beta lactam antimicrobial are prescribed, at least 7 days of therapy is recommended. When women present with more severe systemic symptoms such as fever or pyelonephritis 10–14 days of therapy is the usual recommended duration of treatment.

Men with any presentation of symptomatic infection should be treated initially with a course of 10–14 days. Symptomatic relapse from a prostate source requires a more prolonged course of therapy of 6–12 weeks. A prostate source should be considered when recurrent relapse with the same organism occurs and other urologic abnormalities to explain the recurrence have not been identified (25).

For individuals with chronic indwelling catheters, treatment courses should be limited to as short a duration as possible. In this setting, antimicrobial therapy will

**Table 3** Antimicrobials for treatment of urinary tract infection in elderly populations with normal renal function

Agent	Dose	
	Oral	Parenteral
<b>Penicillins</b>		
Amoxicillin	500 mg tid	1–2 g q6h
Amoxicillin/clavulanic acid	500 mg tid or 875 mg bid	
Piperacillin		3 g q4h
Piperacillin/tazobactam		3.375 g q6h or 4.5 g q8h
<b>Cephalosporins</b>		
Cephalexin	500 mg qid	
Cefazolin		1–2 g q8h
Cefadroxil	1 g qd or bid	
Cefixime	400 mg qd	
Cefuroxime axetil	250 mg bid	
Cefpodoxime proxetil	200 mg bid	
Cefotaxime		1–2 g q8h
Ceftriaxone		1–2 g q12–24h
Ceftazidime		500 mg to 2 g q8h
<b>Fluoroquinolones</b>		
Norfloxacin	400 mg bid	
Ciprofloxacin	250–500 mg bid	400 mg q12h
Extended release	500 mg to 1 g qd	
Ofloxacin	200–400 mg bid	400 mg q12h
Levofloxacin	250 mg q24h	250 mg q24h
<b>Aminoglycosides</b>		
Gentamicin		1–1.5 mg/kg q8h or 4–5 mg/kg q24h
Tobramycin		1–1.5 mg/kg q8h or 4–5 mg/kg q24h
Amikacin		5 mg/kg q8h or 15 mg/kg/q24h
<b>Other</b>		
Aztreonam		1–2 g q6h
Imipenem/cilastatin		500 mg q6h
Meropenem		500 mg q6h–1 g q8h
Ertapenem		1 g q24h
Nitrofurantoin	50–100 mg qid	
Monohydrate/macrocystals	100 mg bid	
Trimethoprim	100 mg bid	
Trimethoprim/sulfamethoxazole	160/800 mg bid	

*qd* once a day; *bid* two times a day; *tid* three times a day; *qid* four times a day; *q* every hour

not prevent bacteriuria but will lead to emergence of more resistant organisms therapy. Hence, if there has been a prompt clinical response, then only 7 days therapy is recommended, so antimicrobial pressure which may promote emergence of more resistant organisms is limited.

In elderly patients, prolonged courses of antimicrobial therapy for treatment of urinary infection are generally discouraged. However, for highly selected patients, long term suppressive therapy may occasionally be appropriate. An individual



with an abnormality of the genitourinary tract that predisposes and cannot be cured is given to recurrent symptomatic urinary infection or progressive renal impairment prolonged antimicrobial therapy to suppress symptoms of infection. For instance, in patients with struvite stones that cannot be removed, continuous antimicrobial therapy will prevent further enlargement of stones and preserve renal function. Suppressive therapy is initiated at the full therapeutic dose. If the clinical response is satisfactory and the urine remains sterile, the dose may subsequently be decreased by half after 2–4 weeks of treatment. It must be emphasized, however, that the use of such prolonged antimicrobial therapy should be infrequent, and initiated only where there are compelling indications.

## Prevention

The extent to which prevention of urinary infection in elderly populations is feasible remains unclear. The very high occurrence of urinary infection is primarily due to genetic predisposition or associated comorbidity, neither of which can be modified. Adequate nutrition, optimal management of comorbidities, and maintenance of maximal function certainly seem reasonable recommendations, but the impact of these interventions in decreasing urinary infection is not known. For a few healthy, ambulatory, elderly women who experience frequent episodes of acute cystitis, the use of long-term low-dose prophylactic antibiotics, a strategy similar to younger female populations, may be effective. Such prophylaxis should only be used in selected women without known urologic abnormalities who are experiencing three or more symptomatic episodes a year. This strategy is not appropriate for institutionalized women, in whom uncomplicated infection is unlikely.

The role of supplemental estrogen therapy in preventing urinary tract infection in postmenopausal women remains controversial. Case control studies and prospective, randomized clinical trials have consistently reported no impact or an increased occurrence of urinary infection with systemic estrogen therapy (2, 26). Thus, oral or transdermal estrogen therapy is not recommended to prevent urinary infection. In some, but not all, prospective randomized trials, topical vaginal estrogen therapy has been reported to decrease urinary tract infection in women with frequent recurrent urinary tract infection (27, 28). Case-control studies evaluating the use of vaginal estrogen therapy have consistently reported no impact or, in fact, an increased risk of infection (2). Thus, topical estrogen therapy presently cannot be endorsed solely for an indication of preventing urinary tract infection.

There has been substantial interest including in the popular press, in the use of “natural antiseptics” such as cranberry juice for the management of urinary infection in elderly populations. Cranberry juice was associated with a decrease in the presence of pyuria with bacteriuria in one long-term care facility (29). However, there was no decrease in overall bacteriuria or in the frequency of symptomatic infections in this study. There is no reason to discourage the use of cranberry juice in non-diabetic elderly populations; however, current evidence does not support a significant benefit for cranberry juice in decreasing the frequency of or complications from urinary infection.

Avoidance of devices such as chronic indwelling catheters or condom catheters will also decrease the frequency of infection. This is not always possible for the individual patient where maintaining adequate bladder emptying and comfort must be balanced with the risks of using such devices. Where indicated, condom catheters should be used rather than chronic indwelling catheters for men, as there is a decreased risk of urinary infection with the external device. Intermittent catheterization is an option for subjects with incontinence and a flaccid bladder. A prospective randomized study in institutionalized men reported that the frequency of infection was similar with clean or sterile intermittent catheterization (30). Thus, clean catheterization, which is less costly, is recommended.

While it may not be feasible to prevent asymptomatic bacteriuria, some symptomatic episodes may be avoided. Strategies that are effective include prophylactic antimicrobials prior to invasive urologic procedures, and optimal catheter care. Specifically, ensuring there is no obstruction to catheter drainage and avoiding catheter trauma will prevent episodes of systemic infection.

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# Bacterial Meningitis and Brain Abscess<sup>1</sup>

Chester Choi

## Key Points

- More cases of bacterial meningitis now occur in older adults, and their outcomes are worse than those seen in younger patients, especially with *Streptococcus pneumoniae* infection.
- The symptoms and signs of bacterial meningitis are not sensitive or specific, particularly in older adults, and, therefore, a lumbar puncture is a key test in diagnosis.
- Early, appropriate antibiotics for bacterial meningitis in conjunction with prior administration of dexamethasone, specifically for *S. pneumoniae* meningitis, are currently the best approach to treatment.
- Vaccination is underutilized but may offer the best means of preventing serious *Streptococcus pneumoniae* infections, including meningitis.
- Brain abscess is a severe complication of extension of local cranial infections or hematogenously disseminated infections; its treatment requires the coordinated efforts of neurosurgeons, critical care physicians, neuroradiologists, and infectious disease specialists to aspirate the lesions and to provide appropriate antibiotic therapy.

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## Epidemiology and Clinical Relevance

Overall, bacterial meningitis appears to be declining in incidence, from 1.9 cases per 100,000 persons to 1.5 per 100,000 as determined by a recent Centers for Disease Control and Prevention (CDC) surveillance study, but more cases are now seen in the older adult population with concomitant high case-fatality rates and significant morbidity. In this CDC and other epidemiologic studies, the increased incidence of bacterial meningitis was noted particularly with etiologic organisms such as *Streptococcus pneumoniae*, *Listeria monocytogenes*, *Streptococcus agalactiae* (group B streptococci), and gram-negative bacilli (1, 2). In contrast, viral meningitis seemed to be a more uncommon infection in the older adult. An epidemiologic surveillance study performed by the CDC in 1995 showed that *S. pneumoniae* accounted for almost 70% of the cases of meningitis in those over the age of 60; the case fatality rate for this organism was 21% (3). Similarly, *L. monocytogenes* accounted for almost 25% of the cases and was associated with a case fatality rate of 15%. Other pathogens such as *Haemophilus influenzae*, *S. agalactiae*, and *Neisseria meningitidis* together accounted for about 6% of cases. The CDC study of cases from 1998 to 2003 showed that the median age for all meningitis patients had risen from 25 to 39 years and that the case fatality rate was highest amongst older adults (28% for those 65 years of age or greater) (1). Data from a 2007 study from the Netherlands confirmed the CDC's findings, showing that 68% of cases in older adults were due to *S. pneumoniae* and complication rates were 72% in older adults versus 57% in younger patients. The overall mortality rate was 34% in older adults versus 13% in younger adults, and the former group tended to die from cardiorespiratory causes as opposed to the neurological deaths from brain herniation seen in the younger population (2). Other earlier estimates of the overall attack rate of bacterial meningitis in individuals over 60 years of age range from 2 to 9 per 100,000 per year, accounting for 1,000–3,000 cases per year in the United States. A summary of these data and case fatality rates for the responsible organisms is shown in Table 1 (3–5).

**Table 1** Surveillance studies of bacterial meningitis in older adults

Organisms	Studies					
	Wenger et al.		Schlech et al.		Schuchat et al.	
	AR	CFR	AR	CFR	AR	CFR
<i>Streptococcus pneumoniae</i>	1.5	31	0.5	54	1.9	20
<i>Listeria monocytogenes</i>	0.5	–	0.1	41	0.6	–
<i>Haemophilus influenzae</i>	0.2	–	0.09	24	0.7	–
<i>Neisseria meningitidis</i>	0.1	–	0.2	29	0.1	–
<i>Streptococcus agalactiae</i>	0.2	51	0.02	23	0.1	18

AR attack rate per 100,000; CFR case fatality rate (percent)

Data from (3–5). (Reprinted with permission.)

## ***Pathogenesis***

The access of bacterial pathogens to the cerebrospinal fluid (CSF) and meninges is generally thought to happen via hematogenous spread or from local invasion from areas of colonization or infection. The ability of bacteria to colonize mucosal surfaces and survive normal host defense mechanisms such as opsonization, complement activation, and phagocytosis are, doubtless, important pathogenic factors. Once organisms gain access to the CSF and meninges, host defenses are relatively meager, and bacteria can freely replicate to large numbers. Inflammatory mediators are activated, leading to increased intracranial pressure, vasogenic edema, altered intracerebral vascular autoregulation, and neuronal apoptosis with resultant cerebral ischemia or infarction, hydrocephalus, subdural effusion or empyema, and sagittal sinus or cortical vein thrombosis. The clinical sequelae of these complications may be manifest as seizures, stroke syndromes, cranial nerve deficits, coma, or death (6–8).

## ***Etiologic Organisms***

In the older adult, the most frequent cause of bacterial meningitis, *S. pneumoniae*, may be recognized as gram-positive diplococci or short chains of cocci with elongation along the axis of division. Serotyping of this organism is based on antigenic differences in the capsular polysaccharides and allows for differentiation into over 84 serotypes, but most disease is caused by a relatively small number of serotypes (1, 3, 4, 7–11) that tend to have larger capsules. The development of resistance to multiple antibiotics, particularly of that to penicillins and to cephalosporins, has significantly complicated treatment. Such resistance to penicillins and cephalosporins is related to alteration of penicillin-binding proteins with subsequent decreased affinity for these antibiotics, but the organism may be concomitantly resistant by other mechanisms to other antibiotics including chloramphenicol and many macrolides and tetracyclines (7, 8).

*L. monocytogenes* is an aerobic, gram-positive bacillus that is often associated with foodborne illness; however, most cases of meningitis from this organism are not directly traceable to the usual food sources such as cheeses, prepared meats, and dairy products. *L. monocytogenes* must be differentiated from diphtheroids, as misidentification or the assumption that the diphtheroid-like organisms represent contaminants has resulted in clinical catastrophes. In contrast to diphtheroids, *L. monocytogenes* manifests beta hemolysis and has a characteristic “end-over-end” tumbling motility. Infections with this organism are often associated with alterations in cell-mediated host immunity but may occur in the absence of recognized immunodeficiencies (8, 9, 12).

*N. meningitidis*, *H. influenzae*, and *S. agalactiae* are less common causes of meningitis in the older adult. Five serotypes (A, B, C, Y, W135) of *N. meningitidis* cause most human disease, which can also include bacteremia or pneumonia. This gram-negative diplococcal organism may cause worsened disease or recurrent

disease in patients with acquired or congenital complement deficiency. Most U.S. strains remain of *N. meningitidis* sensitive to penicillins and cephalosporins, but antibiotic resistance to penicillin has been reported in other countries and, recently, to quinolones in the U.S. (13).

*S. agalactiae* is seen with increased frequency in older adults often in association with chronic conditions such as diabetes mellitus, hepatic or renal failure, or urinary tract infections. In CSF, *S. agalactiae* it may be recognized, as with other streptococci, as gram-positive cocci in chains. *S. agalactiae* is usually beta hemolytic in cultures, and its resistance to trimethoprim–sulfamethoxazole or bacitracin aids in its differentiation from *Streptococcus pyogenes* (10). *H. influenzae*, an uncommon cause of meningitis in older adults, was, overall, previously the most frequent cause of bacterial meningitis, but the effective use in children of the conjugate vaccine for this organism has significantly altered its incidence as a cause of invasive disease including meningitis. *H. influenzae*, appears as a gram-negative coccobacillary organism. The organism's frequent ability to produce a beta lactamase renders it often resistant to antibiotics such as ampicillin, amoxicillin, or penicillin (8).

Aerobic gram-negative bacilli (GNRs) such as *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*, and others may also cause bacterial meningitis in older adults and may be spread by the hematogenous route to the meninges from localized infection such as urinary tract infection, pneumonia, or intra-abdominal infection. They GNRs may also gain access to the meninges by direct invasion, particularly after neurosurgical procedures or traumatic injuries (14). Antibiotic-resistant GNRs and methicillin-resistant *Staphylococcus aureus* (MRSA), seen increasingly in nosocomial settings, may be particularly problematic as causes of bacterial meningitis.

## Clinical Manifestations

The classical presentation of bacterial meningitis includes the symptom triad of fever, nuchal rigidity, and altered mentation. Photophobia is also often experienced by patients with bacterial meningitis. A recent retrospective review of cases in the Netherlands revealed that patients 60 years of age or older had the triad in 58% of cases; however, in previous major reviews of these findings in the older adult, fever was noted in less than 60% in one study and, in another study, nuchal rigidity was found in less than 60% (Table 2) (11, 15).

**Table 2** Frequency of symptoms and signs of meningitis in the older adult

Symptom or sign	Frequency (%)
Fever	59–100
Confusion	57–96
Headache	21–81
Nuchal rigidity	57–92

Source: adapted from (8, 11, 15) (Reprinted with permission.)

The evaluation of nuchal rigidity should assess for limitation of range of motion of the neck in all directions. Limitations to rotation or lateral flexion are seen more frequently with cervical arthritis, and flexion with this condition often results in limitation at the extremes of range of motion; however, meningitis, usually causes immediate resistance to flexion due to the meningeal irritation and muscle spasm. Kernig's sign is determined by passive flexion of the hip and then extension of the knee with resultant extensor spasm at the knee at 135° in the presence of meningeal irritation, whereas Brudzinski's sign is elicited by neck flexion with resultant hip and knee flexion (16).

In a study on acute care and rehabilitation units, Puxty and colleagues found that, in the absence of meningitis, older adults often had nuchal rigidity, Kernig's, and Brudzinski's signs (17). In a later evidence-based review of the rational clinical examination for identifying adults with meningitis, utilizing data predominantly from studies of older adults, the absence of any of the three symptoms of fever, nuchal rigidity, or altered mentation essentially excluded the diagnosis of meningitis; but patients with this diagnosis could have one or more of the findings but not necessarily all three. The presence of two of the three findings carried a 95% sensitivity (18). A single prospective study of 54 patients evaluated the utility of "jolt accentuation" test and found a sensitivity of 97% for this test that involves the rapid (2–3 times per second) alternating horizontal head rotation. No other studies have confirmed the jolt accentuation test or evaluated its specificity (19).

Thus, these physical examination findings are neither specific nor sensitive for diagnosis, particularly in the older adult where fever may be a less common finding in infection, nuchal rigidity may be a result of cervical arthritis or neurological conditions, and altered mentation may be multifactorial, chronic, or due to other infectious or non-infectious causes.

## ***Differential Diagnosis***

A commonly encountered clinical scenario is that of an older adult patient with fever and acutely altered mentation. Infection at a site distant from the meninges such as pneumonia or urinary tract infection is known to be a possible cause with resultant delirium, depressed mentation, or even coma. An evaluation and assessment for the possibility of bacterial meningitis may very well be warranted since the antibiotic choices and dosing may be significantly different for bacterial meningitis and since this disease may be fatal if inadequately treated (20, 21).

In a study of hospitalized patients who did not have a recent neurosurgical procedure and who did not have meningeal signs or headache, nosocomially acquired meningitis was not noted (22). However, for those geriatric patients who develop fever and acute altered mentation either during or prior to hospitalization, one should consider the pre-test likelihood of meningitis in considering the need for lumbar puncture (LP). Some clinically stable patients without meningeal signs or headache, but with an apparent non-meningeal infection, may be treated for the



infection and closely observed without an LP; however, most patients with these symptoms should undergo an LP if it is deemed safe (21, 23). In those with non-central nervous system (CNS) infection, the cause of such depressed mentation is likely increased cytokine levels produced in response to the infective process (24).

The differential diagnosis of bacterial meningitis, with or without meningeal signs, includes those entities capable of causing altered mentation and fever. Conditions that should be considered in the differential diagnosis include brain abscess, encephalitis, subdural empyema, epidural abscess, cancers (either primary or metastatic malignancies of the CNS), cerebrovascular disease, and vasculitis.

## Diagnostic Tests

The lack of specific clinical symptomatology makes the LP the key test for diagnosis of bacterial meningitis, but the possibility of adverse complications, particularly herniation, from the performance of the LP may inhibit its use and has encouraged widespread utilization of computed tomographic (CT) brain scans to assess this risk prior to the LP. Recognizing prior studies which show that a CT scan does not necessarily predict either the safety of an LP or the certainty of herniation, an analysis of the necessity for the CT identified key clinical features at base line that were associated with an abnormal finding; these included age over 60, immunocompromise, a history of CNS disease, and a history of seizures within 1 week prior to presentation. Key clinical findings that might predict an abnormal CT included the following: abnormal level of consciousness, inability to answer two consecutive questions or to follow two consecutive commands correctly, abnormal gaze palsy, abnormal visual fields, presence of facial palsy, arm drift, leg drift, and abnormal language (e.g., aphasia). Absence of these findings had a negative predictive value of 97% for an abnormal CT scan, suggesting a helpful approach to decisions about the need for a CT prior to LP (25).

The LP should be assessed for opening pressure, white blood cell count (WBC), and differential, red blood cell count RBC, protein, and glucose. A Gram stain and culture of the CSF are mandatory. In selected situations, a polymerase chain reaction test for herpes simplex virus should also be obtained, and some CSF may be reserved for other tests for viral etiologies or further encephalitis evaluation; a simultaneous serum glucose should also be obtained as well as a complete blood count with differential and blood cultures (7, 26, 27).

While there is overlap in the CSF findings for various causes of meningitis, most cases of bacterial meningitis result in hypoglycorrachia (CSF glucose less than 40 mg/dl or less than 1/3 of the simultaneous peripheral glucose), neutrophilic predominance and elevated WBCs (more than 500/ml), and protein greater than 150 mg/dl (Table 3). The Gram stain in untreated bacterial meningitis is often positive (approximately 85% of cases), except with *L. monocytogenes* meningitis or gram-negative bacillary meningitis in which the yield on such stains is lowered to approximately 50% (27, 28).

**Table 3** Cerebrospinal fluid findings in meningitis

	Normal CSF	Acute bacterial	Viral	Tuberculous
Opening pressure	6–20 cm H <sub>2</sub> O	Usually elevated	Normal to moderately elevated	Usually elevated
CSF WBC's	0–5 (about 85% lymphs)	Usually several hundred to >60,000, PMN's predominate	5 to a few hundred but may be more than 1,000. Lymphocytes predominate but may be >80% PMN's in the first few days	Usually 25–100, rarely >500. lymphocytes predominate except early stages where PMN's may account for >80% of cells
Protein	18–45 mg/dl	Usually 100–500, occasionally >1,000	Frequently normal or slightly elevated; <100; may show greater elevation in severe cases	Nearly always elevated; usually 100–200 but may be much higher if dynamic block
Glucose	45–80 mg/dl, or 0.6 × serum glucose	Usually 5–40 mg/dl or <0.3 × serum glucose	Usually normal, but can be low with mumps, HSV 2	Usually reduced; <45 in 3/4 of cases
Misc.	For traumatic taps add 1 WBC and 1 mg/dl protein for each 1,000 RBC's	Gram stain + in about 60–80%; Sp = gram + diplococci, Nm = gram neg diplococci, Lm = gram + rods	Usually do not need to find specific causal virus	AFB + stain in <25%, culture + in >2/3 of cases (but may take 4–8 weeks for growth)

Source: adapted from (7, 8, 27, 28). (Reprinted with permission.)

*Sp S. pneumoniae; Nm N. meningitidis; Lm L. monocytogenes; AFB acid-fast bacilli; HSV2 herpes simplex type II; CSF cerebrospinal fluid; PMN's polymorphonuclear neutrophils; RBC's red blood cells; WBC's white blood cells; + positive; cm H<sub>2</sub>O centimeter of water; neg negative*

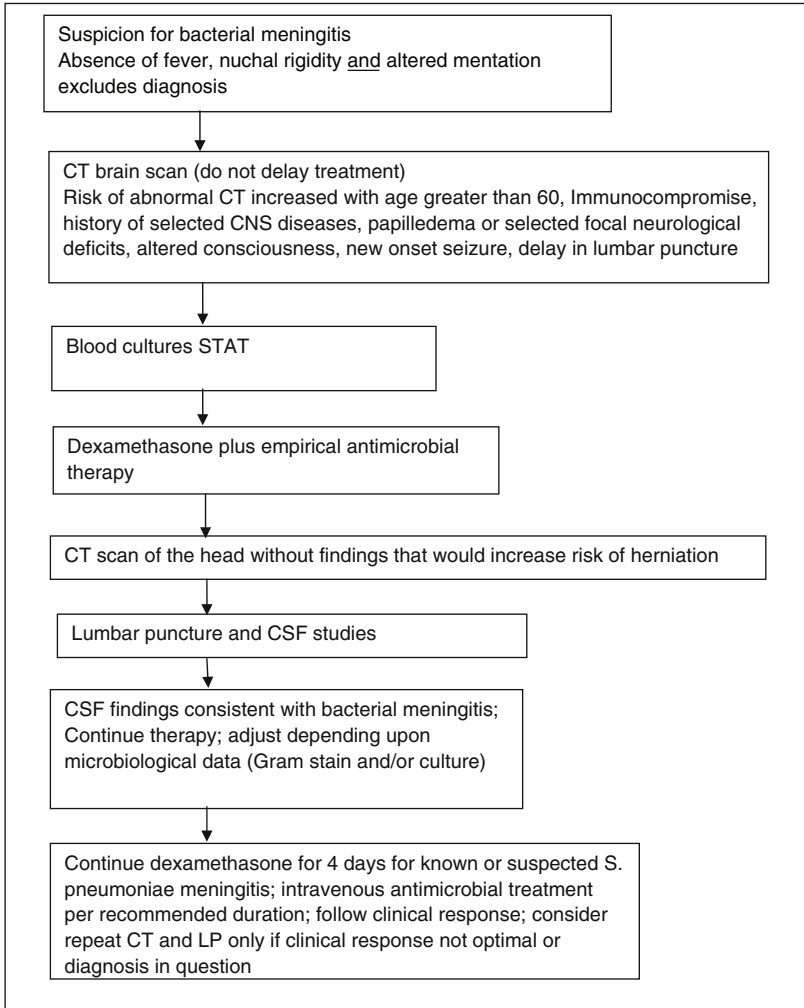
Many patients evaluated for suspected meningitis have received prior antibiotic therapy, and, depending on the particular antibiotic and its dosing, may have altered CSF profiles or lowered Gram stain or culture yields. In such situations, the use of bacterial antigen testing may be of benefit and tests are available for *S. pneumoniae*, *N. meningitidis*, *H. influenzae*, *E. coli*, and *S. agalactiae* are available but not for *L. monocytogenes*. The sensitivities of these tests range from 50 to 75%, while their specificities approach 95–100%. These tests are usually not helpful in the diagnosis of most cases of bacterial meningitis and thus are not routinely obtained; however, they may be quite useful in the particular circumstance of prior antibiotic therapy (7, 27).

Other tests such as procalcitonin or polymerase chain reaction (PCR) testing are under investigation. Elevated procalcitonin levels have been associated with bacterial meningitis. PCR testing could be utilized in a “broad range” fashion, involving a highly conserved bacterial primer, to indicate the presence of bacterial meningitis or in a nested or semi-nested manner to more precisely diagnose the etiologic organism (27, 29, 30).

## Treatment

Since a risk factor, in the study by Hasbun et al., for an abnormal CT scan in patients with meningitis was 60 years of age or older, older adults suspected of having meningitis should undergo CT scans prior to an LP, but therapy (and blood cultures) should not be delayed (see Fig. 1) (25, 26).

Several principles are applied to the choice of antibiotics for treatment of meningitis. Due to the seriousness of this infection and the relative lack of host mechanisms to defend against the replication of bacteria in the CSF and meninges, bactericidal antibiotics are preferred. High doses and frequent or continuous dosing, particularly of cell-wall active agents, are utilized to ensure adequate levels in the CSF of these agents and to maximize their characteristic of time-dependent killing. These high doses need to be maintained throughout the course of treatment. As meningeal inflammation decreases with improvement in the infection or with the administration of dexamethasone, the ability of certain antibiotics to cross the blood–CSF barrier may be affected. This change in the blood–barrier is a particular concern with vancomycin which has variable CSF penetration. Continuous infusion of vancomycin, a strategy uncommonly utilized in the United States, resulted, in one trial of patients who had received dexamethasone for pneumococcal meningitis, in adequate levels of vancomycin in the CSF (31). Further studies of the continuous infusion of vancomycin may be needed. Antibiotics that are capable of crossing the blood–CSF barrier are necessary (Table 4) (32). The issue of penicillin allergy may be encountered in the choice of empirical antibiotic therapy or for more directed therapy. True immediate hypersensitivity type penicillin allergy carries a risk of concomitant cephalosporin or carbapenem allergy, although the latter has been called into question recently. With penicillin hypersensitivity, empirical antibiotic choices could include vancomycin (for *S. pneumoniae*) plus trimethoprim–sulfamethoxazole (for



CT = computed tomographic scan; CNS = central nervous system; CSF = cerebrospinal fluid  
Source: adapted from reference 26  
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**Fig. 1** Management algorithm for older adults with suspected bacterial meningitis. *CT* computed tomographic scan; *CNS* central nervous system; *CSF* cerebrospinal fluid. Source: adapted from (26) (Reprinted with permission.)

*L. monocytogenes*) (26). Listed in Table 5 are antibiotic recommendations for the treatment of specific bacteria and for the empirical treatment of these bacteria until such specific microbiological data is obtained (26, 33).

Despite the use of effective antibiotics, outcomes from the treatment of bacterial meningitis have not changed, and a number of investigators sought adjunctive therapy that might be beneficial. Earlier studies in children with *H. influenzae*

**Table 4** Antibiotic penetration of cerebrospinal fluid

Excellent	Good (with inflammation)	Poor or negligible
Rifampin	Penicillins	Most first- and second-generation cephalosporins
TMP–SMZ	Third-generation cephalosporins	Aminoglycosides Tobramycin Gentamicin
Chloramphenicol	Cefuroxime	
Metronidazole	Vancomycin (variable) Erythromycin (variable) Tetracyclines (variable)	
Quinolones <sup>a</sup>		

TMP–SMZ Trimethoprim–sulfamethoxazole

Excellent: >15–20% penetration

Good: 5–20% penetration

Poor or negligible: <1–5% penetration

Source: adapted from (8, 32, 33). (Reprinted with permission.)

<sup>a</sup>Limited data on optimal dosage and clinical outcomes for meningitis

**Table 5** Recommendations for antimicrobial therapy in older adults

Organism	Antibiotic	Total daily dose
Empirical treatment for bacterial meningitis	Cefotaxime or Ceftriaxone plus Ampicillin plus Vancomycin	8–12 g 4–6 g 12 g 2 g
Post neurosurgery	Vancomycin plus Cefepime or Ceftazidime	2 g 6 g 6 g
CSF shunt infection <sup>a</sup>	Vancomycin plus Cefepime	2 g 6 g
<i>Streptococcus pneumoniae</i> (penicillin sensitive)	Penicillin G	20–24 million units
<i>Streptococcus pneumoniae</i> (cefotaxime, ceftriaxone sensitive)	Cefotaxime or Ceftriaxone	8–12 g 4–6 g
<i>Streptococcus pneumoniae</i> (cefotaxime, ceftriaxone resistant) <sup>a</sup>	Vancomycin	2 g
<i>Listeria monocytogenes</i>	Ampicillin Plus an aminoglycoside: Gentamicin, tobramycin Amikacin	12 g 5 mg/kg 15 mg/kg
(If penicillin allergic)	TMP–SMZ	10–20 mg/kg
<i>Neisseria meningitidis</i>	Penicillin G or Ampicillin	20–24 million units 12 g
<i>Haemophilus influenzae</i>	Cefotaxime or Ceftriaxone	8–12 g 4–6 g
Enterobacteriaceae (gram-negative bacilli)	Cefotaxime or Ceftriaxone	8–12 g 4–6 g
(If <i>Pseudomonas</i> suspected) <sup>b</sup>	Ceftazidime or Cefepime	6 g 6 g
(If ESBL producer)	Meropenem	6 g
<i>Staphylococcus aureus</i> (methicillin sensitive)	Nafcillin or oxacillin	8–12 g
<i>Staphylococcus aureus</i> (methicillin resistant)	Vancomycin	2 g

ESBL extended-spectrum beta lactamase

Source: adapted from (26, 33). (Reprinted with permission.)

<sup>a</sup>Consider addition of rifampin 600 mg/day

<sup>b</sup>Consider addition of an anti-pseudomonal aminoglycoside

meningitis demonstrated the efficacy of adjunctive corticosteroid therapy, and a subsequent study in the Netherlands showed the benefit for high-dose dexamethasone therapy that was given prior to the institution of antibiotics (34). This Netherland study showed the benefit for the administration of dexamethasone only for *S. pneumoniae* meningitis; in addition, patients treated in this study were not infected with penicillin-resistant *S. pneumoniae*, simplifying the antibiotic regimen and avoiding the need for vancomycin, which might have decreased CSF penetration in the face of corticosteroid therapy. The current practice guidelines of the Infectious Diseases Society of America (IDSA) for bacterial meningitis advocate the use of empirical dexamethasone adjunctive therapy prior to the administration of antibiotics, and they also indicate continuation of the corticosteroid therapy for 4 days for patients shown to have *S. pneumoniae* (26). A subsequent study of adult meningitis patients in Denmark demonstrated the benefit of early corticosteroid therapy with unfavorable outcomes in only 17% of early corticosteroid therapy patients as compared to 42% in the non-corticosteroid group ( $p < 0.05$ ) (35).

The treatment of antibiotic-resistant GNRs and MRSA, usually encountered in post trauma or post neurosurgery settings, is more problematic as the penetration of newer antibiotics into the CSF is less well studied, and there are limited clinical studies on their efficacy for the treatment of bacterial meningitis. For MRSA, vancomycin would be the drug of choice. Although linezolid it achieves adequate CSF levels, there is much less clinical experience with the use of linezolid for MRSA meningitis. Daptomycin, another drug active against MRSA, appears to be much less effective in treating CNS infections with this organism. Problematic resistant GNRs include *Pseudomonas aeruginosa*, *Acinetobacter* species, and extended-spectrum beta-lactamase-producing *E. coli*, *Klebsiella*, or *Enterobacter*. For *Pseudomonas*, cephalosporins such as ceftazidime or cefepime are usually effective. For the beta-lactamase-producing group of organisms, a carbapenem such as meropenem is often chosen and preferred over imipenem–cilastatin as meropenem appears to have less propensity to cause seizures. In the case of *Acinetobacter*, one must determine its antibiotic sensitivity as some strains are sensitive to carbapenems or cephalosporins, but some are highly resistant and susceptible only to selected aminoglycosides, colistin, polymyxin B, or tigecycline. There is little clinical experience in the use of this latter drug (tigecycline) for bacterial meningitis; it also has little efficacy against *Pseudomonas* or *Proteus* species. Polymyxin B has poor CNS penetration. Colistin has occasionally been used for *Acinetobacter* or resistant pseudomonal meningitis and is often combined with intrathecal amikacin if in vitro data suggest susceptibility (36).

The duration of treatment for bacterial meningitis has not been established in comparative trials, but the following are part of the IDSA practice guidelines. In general, *S. pneumoniae* should be treated for 10–14 days, *L. monocytogenes* for at least 21 days, aerobic gram-negative bacilli for at least 21 days, *S. agalactiae* for 14–21 days and *H. influenzae* or *N. meningitidis* for 7 days. Until further data are available, patients should be treated with intravenous therapy for the full recommended duration. An end of treatment LP or repeat LP is generally not necessary unless there are clinical findings suggesting failure of therapy to meningitis or patient's failure to respond in 48 h (26, 33, 37).

## Prevention

Since a significant number of bacterial meningitis cases in the older adult are caused by *S. pneumoniae* and since this organism seems to result in a worsened outcome, its prevention should be a high priority for clinicians. Data from the CDC demonstrate that only a little more than half of adults age 65 years and older have ever received pneumococcal vaccination and that the rate is somewhat higher for those 75 or older (38). The newer, conjugated *S. pneumoniae* vaccine, has demonstrated a reduction in invasive pneumococcal disease in vaccine recipients (children) but also in non-vaccinated adults, raising the possibility that *S. pneumoniae* may be communicated from children to exposed, susceptible adults (39). This transmission of *S. pneumoniae* may also explain the peaks in invasive pneumococcal disease that occur seasonally. Current quality improvement measures have targeted improved vaccination as a major goal.

The prognosis, both in terms of mortality and morbidity as graded by the Glasgow Outcomes Scale (GOS) of bacterial meningitis, is worse in older adults, in those with *S. pneumoniae* meningitis, and in those with a delay in initiation of antibiotic therapy (40–42). A bedside prognostic scoring algorithm that may be able to predict an unfavorable outcome of a GOS score of 4 or less has been proposed for use on presentation of patients with meningitis. Key factors in this prognostic scale include age, tachycardia (heart rate greater than 120 beats per minute), a low Glasgow Coma Scale (GCS) score, cranial nerve palsy, a low CSF leukocyte count (less than 1,000 cells/ml), and a Gram stain indicative of gram-positive cocci (43).

In the older adult, when close household exposure has occurred or in situations of mucosal exposure to potentially infectious secretions or aerosols from the index case, antibiotic prophylaxis is occasionally needed in the prevention of *N. meningitidis* meningitis. Regimens for prophylaxis include rifampin 600 mg orally twice daily for 2 days or ciprofloxacin 500 mg orally as a single dose are recommended. Since fluoroquinolone resistance has recently been noted, the latter (ciprofloxacin) should be used only if regional antibiotic sensitivity data suggest its efficacy (13).

## Brain Abscess

### *Epidemiology and Clinical Relevance*

No large series are available to better define the incidence of brain abscess specifically in older adults, but such abscesses are problematic in the elderly, and must be considered in the differential diagnosis of headache and of altered mentation. Recognizing bacterial brain abscess and differentiating this from bacterial meningitis is essential, as the two entities may require different diagnostic evaluations and antibiotic and surgical interventions. The median age of affected patients is 30–40 years. Prior to the advent of CT scanning, case fatality rates were in the 30–60% range but now they range from 0 to 24% (44, 45). Rosenblum and co-authors reported a 44% mortality

rate in the 3 years prior to the availability of CT scanning and no mortalities in the 3 years after the availability at their institution, emphasizing the importance of such scans for early diagnosis, treatment, and improved outcomes (46). Recent epidemiological studies have demonstrated an increase in the number of cases due to prior surgery and a decrease in the number of otogenic origin (47).

## ***Etiology***

Brain abscesses are often divided according to their typical anatomic or pathophysiologic source; the microbial etiologies differ somewhat by site, this division may also aid in the selection of empirical antibiotic therapy. These sites or modes of acquisition include (1) paranasal sinuses, (2) otogenic infections, (3) hematogenous, and (4) post trauma or postoperative (Table 6 lists these sites, their related organisms, and antibiotics effective versus these pathogens (44)); however, up to 20–30% of brain abscesses are classified as “cryptic” because no apparent source can be discerned. Of particular importance is the finding that *Bacteroides fragilis* may be found in temporal lobe or cerebellar abscesses of otogenic origin. The *Bacteroides fragilis* organism is frequently resistant to penicillin. Those abscesses of hematogenous or “metastatic” spread are commonly multiple and may involve any lobe but are often distributed in the areas served by the middle cerebral artery. The organisms involved with this subgroup are diverse and depend upon the originating source. The abscesses due to endocarditis may often involve *S. aureus*, including MRSA or streptococci. Other organisms of particular concern in brain abscesses include *Nocardia* species and *Toxoplasma gondii* seen in immunocompromised hosts (48, 49). Brain abscess accounts for about 10% of CNS infections caused by *L. monocytogenes*, and about 85% of listerial brain abscess patients have underlying immune compromise (48–50).

## ***Pathophysiology***

The brain appears to be relatively resistant to infection, as evidenced by the number of penetrating foreign body injuries that can result in abscess but which often do not. Others have speculated that the brain’s relative resistance may be due to the blood–brain barrier and to the relatively abundant blood supply to much of the brain (44, 48).

The genesis of a brain abscess has been studied in animal models and correlated with patient CT scans. Brain abscess development has been divided into four chronological and histological stages: (1) the early cerebritis stage (days 1–3 after inoculation of organisms) characterized by a focal area of inflammation and edema, (2) the late cerebritis stage (days 4–9) with expansion of the inflammation and development of central necrosis, (3) the early capsule stage (days 10–14) with appearance of peripheral gliosis and fibrosis, and (4) the late capsule stage (beyond 14 days) in which host defenses form to wall off the abscess and a well formed capsule develops (44).



**Table 6** Brain abscess in adults: microbiology and empirical antimicrobial therapy

Source	Abscess site	Typical bacteria	Empirical therapy
Paranasal sinuses	Frontal lobe	Streptococci (especially <i>S. milleri</i> group) Aerobic streptococci <i>Bacteroides</i> (non-fragilis) <i>Fusobacterium</i> species <i>Streptococcus</i> species Enterobacteriaceae <i>Bacteroides</i> (including <i>B. fragilis</i> )	Penicillin or ceftriaxone or cefotaxime plus metronidazole
Orogenic	Temporal lobe Cerebellum	Enterobacteriaceae <i>Bacteroides</i> (including <i>B. fragilis</i> )	Penicillin plus metronidazole plus ceftazidime
Hematogenous spread	Multiple lesions, especially in middle cerebral artery distribution	Depends on source Endocarditis ( <i>Staphylococcus aureus</i> , viridans streptococci) Urinary tract (Enterobacteriaceae, <i>Pseudomonas</i> ) Intra-abdominal ( <i>Streptococcus</i> species, enterobacteriaceae, anaerobes including <i>B. fragilis</i> ) Lung abscess ( <i>Streptococcus</i> species, <i>Actinomyces</i> species, <i>Fusobacterium</i> species) <i>Staphylococcus aureus</i> <i>Clostridium</i> species Enterobacteriaceae <i>Staphylococcus aureus</i> Coagulase-negative staphylococci Enterobacteriaceae <i>Pseudomonas</i>	Oxacillin or nafcillin (substitute or add vancomycin if methicillin resistant <i>S. aureus</i> suspected) plus metronidazole plus cefotaxime or ceftriaxone
Penetrating trauma	Depends on site of wound		Vancomycin plus ceftriaxone or cefotaxime
Postoperative	Depends on site of surgery		Vancomycin plus ceftazidime

Adapted with permission from (44)

Recommended antibiotic dosages (may need adjustment for renal or hepatic disease)

Penicillin: 2–4 million units iv q4h; metronidazole: 500 mg iv q6h; cefotaxime: 1–2 g iv q4–8h, maximum dose 12 g/day; ceftriaxone 2 g iv q12h; ceftazidime: 1–2 g iv q4–8h, maximum dose 12 g/day; nafcillin or oxacillin: 2 g iv q4h; Vancomycin: 1 g iv q12h

## Clinical Manifestations

Patients with brain abscess generally complain of a headache, which often may be unilateral, dull, and aching in character and is typically of a chronic, subacute, or insidious nature. A rapidly developing, severe headache may be caused by a fulminant brain abscess but is more often due to acute meningitis or other causes (45, 48, 49, 51). Symptoms other than headache are inconsistently present and may vary depending upon the location of the abscess. Fever is noted in as few as 40% of patients in some series and altered mentation may or may not be present. Focal neurological findings are noted in only about one-third to one-half of patients. Medical attention may be mistakenly focused on the local source infection rather than on a specific search for brain abscess. The variability of these symptoms and the sometimes insidious onset leads to delays in diagnosis that may adversely affect outcome (44, 48–50). The major differential diagnosis in older adults would be a brain tumor and cerebrovascular accident.

Patients with frontal lobe abscesses may manifest headache, drowsiness, inattention, hemiparesis, and a motor speech disorder. Those with cerebellar abscesses may have ataxia, nystagmus, vomiting, and dysmetria. Temporal lobe abscesses may result in ipsilateral headaches and aphasia (if the lesion is in the dominant hemisphere); in some patients, a visual field defect has been the only presenting sign of a temporal lobe lesion. Abscesses of the brain stem may cause facial weakness, fever, hemiparesis, dysphagia, or vomiting (48).

## Diagnostic Tests

Routine laboratory testing may not be helpful in leading to the diagnosis of brain abscess. The WBCs may be normal; blood cultures should be performed, as they may yield the etiologic organism(s) but are often negative. The key diagnostic test is brain imaging, ideally with a magnetic resonance imaging (MRI), which is somewhat more sensitive than is a CT scan. The MRI of a “mature” brain abscess may demonstrate a mass lesion with decreased central signal intensity on T1 weighted images and increased signal intensity on T2 images (“filling-in” of the abscess). The capsule surrounding the abscess tends to be thicker on the cortical (non-ventricular) side and also tends to have a smoother surface than that of many tumors, but the differentiation between these two entities can be difficult on radiological grounds alone and aspiration may be needed (44, 48).

An LP is contraindicated if a brain abscess is suspected or proven, as there is an increased risk of herniation. In addition, CSF studies in cases of brain abscess may be abnormal but do not usually add to the useful diagnostic information or microbiologic data. Except for small, deep, multiple abscesses difficult or dangerous to access, most brain abscesses should be aspirated for microbiological diagnosis. Such aspirations may be done by a “free-hand” approach under CT guidance or for

deeper, smaller, or less accessible abscesses, by stereotactic neurosurgical procedures; however, the timing of the aspiration is key since attempts to aspirate early lesions in the cerebritis stage are associated with an increased risk of hemorrhage and are less likely to yield the responsible organisms in the absence of pus. It may be necessary to perform serial CT or MRI scans every few days to gauge the earliest opportunity for aspiration to produce the best yield (44).

If the microbiology of the abscess can be determined and appropriate antibiotic therapy instituted, then further surgical intervention may not be necessary except in instances of failure to respond to the antibiotics or situations of dual diagnoses (infection plus cancer for instance). No evidence-based studies are available to guide the duration of therapy, but most patients are treated for a minimum of 6 weeks of intravenous therapy, and many receive a subsequent 2- to 3-month course of oral treatment. Serial CT brain scans or MRIs are generally performed to monitor the effects of therapy. In occasional cases, excisional procedures to remove the abscess are required, but neurological sequelae may be increased by the more extensive procedure. Rupture of the abscess into the ventricular space may be heralded by nuchal rigidity and worsened headache. This catastrophic complication is usually treated with ventricular drainage but carries a worsened prognosis (44, 48).

The initial antibiotic therapy should take into account the likely source of infection but generally includes ceftriaxone or cefotaxime plus metronidazole (52). These agents have activity versus most streptococci, anaerobes, including *B. fragilis* and many aerobic GNRs. If staphylococci are suspected, then vancomycin should be utilized to ensure coverage for MRSA. Vancomycin appears to have good penetration into cerebral abscesses. If the abscess is suspected to be the result of a nosocomially acquired infection that might involve *P. aeruginosa*, *Acinetobacter*, or ESBL-producing GNRs, then meropenem may need to be substituted for ceftriaxone (49).

Specific antibiotic treatment should be directed by microbiological data, and appropriate intravenous antibiotic therapy should be extended over a 6-week course, although there are no evidence-based studies to direct the duration of treatment. When possible, depending upon the responsible pathogens, to ensure complete eradication of organisms in this loculated collection of pus, many clinicians continue a further 2–3 months of oral antibiotic therapy. Most cases do not require surgical removal of the abscess, as the removal may be associated with worse neurological sequelae (44, 48).

Outcome studies have highlighted (1) the rapidity of progression of disease prior to hospitalization, (2) delays in recognition of the disease, and (3) neurological status on presentation (worsened GCS) as relative predictors of a poorer outcome (48, 53, 54).

Some patients may manifest increased intracranial pressure and require interventions such as high-dose dexamethasone, hyperventilation, or mannitol. In addition, patients may have persistent or recurrent seizures. The coordinated efforts of neurosurgeons, neurologists, neuroradiologists, critical care specialists, and infectious disease specialists are essential for the best management of such complicated patients.

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## Suggested Reading

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# Osteomyelitis and Septic Arthritis

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## Key Points

- Regardless of the route of infection, *Staphylococcus aureus* is the most common pathogen implicated in osteomyelitis in the adult and elderly population.
- Acute osteomyelitis usually responds to antimicrobials alone; however, the elderly typically present with chronic osteomyelitis, which often requires concomitant surgical management and long-term wound care.
- Because of peripheral vascular disease, neuropathy, and age-related changes in immune response, infections such as osteomyelitis and septic arthritis are more likely to have subtle or atypical symptoms and signs in the elderly as compared with other age groups.
- Septic arthritis often presents as an acute monoarthritis and is a medical emergency that requires arthrocentesis for diagnosis and treatment.
- Older adults are more likely to present with non-gonococcal infectious arthritis occurring as a result of hematogenous spread to a previously damaged joint.

## Osteomyelitis

### *Epidemiology and Clinical Relevance*

Osteomyelitis is a direct infection of bone resulting in inflammation, destruction, and new bone formation. Intact bone is usually resistant to infection, making the diagnosis of osteomyelitis rare in most healthy adults (1); however, certain risk factors such as trauma, instrumentation, or intravenous drug use are associated with loss of bone integrity and these factors increase the likelihood of infection. Long-standing conditions, common in older adults, such as vascular insufficiency, neu-

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ropathy, or pressure ulcers, and immunocompromised states such as diabetes mellitus, end-stage renal disease, or cancer can further increase the risk of osteomyelitis.

Osteomyelitis is commonly classified according to the duration of infection (acute vs. chronic) and the mechanism of infection such as hematogenous spread, contiguous extension of an infection, or vascular insufficiency causing osteonecrosis and super-infection. The terms *acute* and *chronic* describe the time course of disease as well as the possible complications. Acute osteomyelitis occurs over a period of days whereas chronic osteomyelitis evolves gradually over a period of weeks to months and leads to the formation of abscesses, dead bone, and sinus tracts. Chronic osteomyelitis is often resistant to antibiotic treatment alone and requires concurrent surgical debridement or revascularization.

Regardless of the route of infections, the most common infective agent is *Staphylococcus aureus*. The organism has evolved several mechanisms to promote adhesion and invasion, as well as survival within osteoclasts (2). Other microorganisms

**Table 1** Common pathogens involved in osteomyelitis<sup>a</sup>

Pathogen	Common Clinical Association
<i>Staphylococcus aureus</i> (methicillin-sensitive)	Most common pathogen
<i>S. aureus</i> (methicillin-resistant)	Community acquired as well as nosocomial
Coagulase-negative <i>staphylococci</i>	Prosthetic joint infection Post-surgical osteomyelitis
<i>Propionibacterium</i> spp.	Prosthetic joint infection
<i>Streptococcus</i> spp.	Pressure ulcers, Foot ulcers Oropharyngeal source of infection
Enteric gram-negatives	Genitourinary/ gastrointestinal source
Enterobacteriaceae	Nosocomial Infections
<i>Serratia</i> spp.	Nosocomial Infections Intravenous drug use
<i>Pseudomonas aeruginosa</i>	Nosocomial Infection Puncture wounds Wounds soaked in water Intravenous drug use Long-standing in-dwelling catheters
<i>Salmonella</i> spp.	Patients with sickle cell disease
Anaerobic organisms	Part of polymicrobial infections Oropharyngeal, gastrointestinal source Pressure ulcers, Foot ulcers
<i>Candida</i> spp.	Nosocomial infection in immunocompromised host Intravenous drug use Long-standing in-dwelling catheters
<i>Pasturella multocida</i>	Osteomyelitis due to animal bite
<i>Mycobacteria tuberculosis</i>	At-risk population Patients with latent tuberculosis
<i>Brucella</i> spp, <i>Coxiella burnetii</i> , blastomycosis histoplasmosis, coccidiomycosis	Patients from endemic areas
Atypical mycobacteria, <i>Bartonella quintana</i>	Immunocompromised host
<i>B. henselae</i> , <i>Aspergillus</i>	HIV patient

<sup>a</sup>Adapted from (1)



including *Mycobacteria* and fungi occur in specific clinical scenarios (see Table 1). Once the inoculum invades the bone, cytokines are released and attract acute inflammatory mediators. The accompanying inflammation causes vascular edema and localized thrombosis that result in impaired blood flow to the bone.

As the ensuing vascular compromise and inflammation cause cell death, osteonecrosis, and the formation of abscesses and sinus tracts, acute osteomyelitis evolves into chronic osteomyelitis over the course of weeks to months. It is these fragments of dead bone, called the sequestra, and surrounding vascular compromise that makes chronic osteomyelitis highly resistant to treatment with antimicrobials alone. Bacteria can further evade eradication by encasing itself in a protective biofilm. New bone also starts to form from the remaining live bone or from the intact periosteum surrounding infected dead bone. This involucrum may gradually incorporate into live bone; its irregular surface may allow purulent fluid to track into the surrounding soft tissue forming sinus tracts.

During the infection, the remaining live bone can also become osteoporotic, and the risk of fractures increases (3). As the infection resolves, the bone may strengthen but does so slowly over the course of months. Care should be taken in the elderly to avoid excessive strain on these weak, fragile bones.

### **Contiguous Focus Osteomyelitis**

Osteomyelitis can occur by contiguous extension of an adjacent focus of infection. Common causes include ear and sinus infections, cellulitis, or an infected foreign body. Direct inoculation of the bone can occur during surgery, with epidural or intrathecal injections, after trauma, or as a result of a fracture.

In the elderly, due to direct extension, infected pressure ulcers are an increasingly common source of osteomyelitis (see also chapter “Skin and Soft Tissues Infections”). Osteomyelitis has been reported to complicate about 17% of infected pressure ulcers (4). Because these infections are associated with poor perfusion and necrosis, such infections are generally polymicrobial in nature. Depending on the common organisms found in the adjacent source of infection, broad-spectrum antibiotics that cover gram-positives and gram-negatives, as well as anaerobic bacteria are often required.

### **Hematogenous Osteomyelitis**

Osteomyelitis can occur after a period of bacteremia or fungemia. Osteomyelitis of the long bones is more common in children than in the adult population. In the adult and in the elderly, the vertebrae, with their abundant and slow-moving blood supply, are the more likely site of infection (5). The lumbar spine is the most commonly affected followed by the thoracic and the cervical spine. The infection can further spread to adjacent vertebra or into the meninges.

Bacteria can be introduced into the bloodstream as a result of the following: urinary tract infection, pneumonia, intravenous drug use, intravascular catheters, or a perforation of the gastrointestinal tract. Poor dentition can also cause transient bacteremia leading to osteomyelitis (as well as infective endocarditis). Although such cases of osteomyelitis are associated with blood-borne pathogens, the organism is not always isolated from blood cultures.

Most forms of hematogenous osteomyelitis are due to a single pathogen. Exceptions include osteomyelitis associated with intravenous drug use which tends to be polymicrobial. *S. aureus* is the most common isolate. In the elderly, due to a genitourinary or gastrointestinal source, gram-negative bacteria are an increasing source of infection. Due to *Candida* species, indwelling catheters, especially in the immunocompromised, may lead to infection. Mycobacteria or fungi should be considered in specific situations.

### **Osteomyelitis Due to Vascular Insufficiency**

Osteomyelitis as a result of vascular insufficiency is a common concern in older adults who are more likely to have peripheral vascular disease or diabetes mellitus. Such infections commonly involve the distal limbs, especially the small bones of the feet. Lack of blood flow can result in osteonecrosis as well as ulceration and superinfection of the overlying skin, which can then spread to bone. In patients with sensory deficits from peripheral neuropathy, areas of skin breakdown can go unnoticed, and patients often fail to seek care early.

Osteomyelitis from vascular insufficiency is often polymicrobial and involves gram-positive, gram-negative, and anaerobic bacteria; however, even with the correct antimicrobial drugs and surgical debridement, healing is limited by compromised blood flow. Surgical revascularization of the larger arteries may restore perfusion and improve healing. Patients with small vessel disease not amenable to revascularization may require chronic suppressive antimicrobial therapy or amputation.

### ***Clinical Manifestations***

The clinical evaluation alone is a poor indicator of osteomyelitis with a sensitivity and specificity of 33% and 60% respectively (4). Patients with osteomyelitis may note gradual onset of dull pain overlying the bone. Often, the patients may have attributed the pain to a benign musculoskeletal injury for several months before seeking help. Fever is typically absent, especially in patients with chronic osteomyelitis. Osteomyelitis may present as bone pain in patients being treated for concomitant infections such as a urinary tract infection. New onset instability of a prosthetic joint or of soft tissue infections and pressure ulcers that do not respond to treatment may be an indicator of underlying bone infection. Infections

of the sternum or ribs can cause chest pain that can be mistaken for cardiac or pulmonary disease. In patients with sensory deficits or neuropathies, discomfort may not always be elicited.

Patients may present with an open wound or sinus tract. Underlying osteomyelitis may occur even in pressure ulcers with an overlying eschar. The presence of a wound that “probes to bone” is not synonymous with osteomyelitis, as approximately 50% of pressure ulcers with exposed bone do not demonstrate osteomyelitis on biopsy (4, 6).

The patient with vertebral osteomyelitis may have, on physical examination, local tenderness over the spine, reduced spinal mobility, and paravertebral muscle spasms. Vertebral osteomyelitis can cause adjacent soft tissue infection that may be suggested by the clinical examination. Extension posteriorly into the epidural space leads to epidural abscess and the patient may note focal or severe back pain, radiculopathy, muscle weakness, sensory abnormalities, bladder or bowel dysfunction, or even paralysis. If the patient with vertebral osteomyelitis has pain when the hip is passively extended or actively flexed against resistance, then a limp or flexion deformity of the involved hip, a psoas abscess should be considered.

The symptoms and signs of osteomyelitis in the geriatric population are more likely to be subtle or atypical with minimal or absent fever, leukocytosis, and signs of local inflammation. In the elderly patient with cognitive impairment, the ability to communicate symptoms is limited, and such patients may instead present with delirium or a reluctance to move, sit, or stand.

## ***Diagnostic Tests***

### **Laboratory Tests**

Laboratory tests are often suggestive but not diagnostic of osteomyelitis. Most patients with osteomyelitis will have a normal white blood cell count. The levels of alkaline phosphatase and calcium are normal as well. Due to hematogenous spread, blood cultures may be useful in diagnosing osteomyelitis.

Markers of inflammation such as the erythrocyte sedimentation rate (ESR) or the C-reactive protein (CRP) are often significantly elevated in patients with osteomyelitis; however, these tests are nonspecific and therefore may be more useful in excluding the diagnosis. An elevated ESR or CRP may also be useful in monitoring response to treatment. A persistently elevated ESR can indicate treatment failure and a need for further intervention. Studies have shown about 33–50% of patients over the age of 60 who did not have a significant decline in ESR after 1 month of treatment went on to have successful eradication (7). The normal range for the ESR increases with age; any obtained value should be considered in the context of the patient’s age. Often after several weeks of therapy, ESR declines slowly. CRP may be a more reliable indicator of therapeutic response, as the levels normalize much more quickly and often within a week of appropriate therapy (8).

## Imaging

Plain radiographs can reveal evidence of osteomyelitis within 10–21 days of infection. Common findings on radiographs include soft tissue swelling, bone destruction, periosteal reaction, or a change in the size of the joint space. Persistent inflammatory erosion into bone can lead to cortical destruction and subsequent lucencies within the cortex. In patients with vertebral osteomyelitis, involvement of adjacent vertebrae and loss of intravertebral disc space may be apparent. The sensitivity of plain radiographs for detecting osteomyelitis ranges from 43 to 75%; the specificity can range from 75 to 83% (9). Because of this modest ability to detect infection, other imaging modalities are often required in the evaluation of osteomyelitis.

Computed tomography (CT) scans can detect sinus tracts, sequestra, gas, destruction of cortical bone, soft tissue inflammation, and periosteal reaction. Because the images are prone to artifacts, due to metal or the presence of bone, the role of CT scans in diagnosing osteomyelitis has been largely replaced by magnetic resonance imaging (MRI).

An MRI can provide detailed information about bone and the surrounding soft tissue. The presence of fibrosis, necrosis, and scarring can help differentiate between acute and chronic osteomyelitis. An MRI can also define areas of edema, abscess formation, and joint space involvement. On occasion, an MRI may fail to distinguish between osteomyelitis, neoplasm, or Charcot's joint. Most recent studies suggest that an MRI has a sensitivity of 82–100% and a specificity of 75–96% (9).

Ultrasound studies have limited utility in evaluating osteomyelitis and are commonly being used to evaluate for pockets of fluid. Recent studies suggest that positron emission tomography (PET) combined with a CT may have a role in the evaluation and management of osteomyelitis (10).

Because nuclear imaging is able to evaluate the whole body at once, it can identify potential areas of osteomyelitis that are clinically asymptomatic. Nuclear imaging studies have limitations in localizing infection in areas where multiple bones are in close contact such as the foot. Patients with vascular disease may also have false-negative studies as a result of poor delivery of the isotope (9). For older patients with chronic kidney disease, nuclear imaging may be the study of choice, as nephrogenic systemic fibrosis has been associated with the use of gadolinium-containing contrast agents during MRI studies, and contrast-induced nephrotoxicity can occur with iodinated contrast medium (11). Three-phase bone scans use labeled technetium to detect areas of increased osteoblastic activity. Bone scans provide limited information on the extent of infection and the presence of abscesses or sinus tracts. Furthermore, the specificity of the bone scan decreases in patients with other skeletal abnormalities such as a fracture, pressure ulcer, Charcot's joint, or recent orthopedic surgery (4, 9). Gallium scans are more specific when compared with three-phase bone scans, but these scans take longer to complete, as imaging is performed 24–48 h after injection. White blood cell (WBC) scans use labeled leukocytes to localize infection, and the specificity and sensitivity of WBC scans are higher than that of bone scans for the detection of osteomyelitis.

However, the WBC scan is time-consuming and technically more challenging, as it requires drawing blood from the patient beforehand and labeling white blood cells.

### **Bone Biopsy**

Despite radiographic evidence of osteomyelitis, a bone biopsy is typically required to confirm the diagnosis and cultures from the biopsy and can identify the infective organism as well. Samples can be obtained by open biopsy or CT-guided biopsy in order to obtain an adequate amount of tissue. Cultures from a superficial swab of the lesion are not useful in directing antibiotic therapy as they often identify colonizing organisms. In patients with chronic osteomyelitis, superficial swabs and aspirates, when compared to bone cultures, were accurate only 30% of the time (12).

### ***Treatment***

Often, antimicrobial therapy alone is adequate for patients with uncomplicated acute osteomyelitis. Most adult patients, including the elderly, often present with chronic disease, which may require concomitant surgical intervention. Optimal treatment of chronic osteomyelitis requires a multidisciplinary approach with input from infectious disease specialists, surgeons, and wound care specialists.

Patients with vertebral osteomyelitis initially may need to be placed on bed rest until the pain resolves. Aggressive deep venous thrombosis prophylaxis and low-level physical therapy should be instituted. When the patient resumes mobility, a fitted back brace may provide pain relief and support until therapy is complete (3). Given the risk for osteoporosis, calcium, vitamin D, and bisphosphonates should be considered. The role of hyperbaric oxygen therapy in the management of chronic osteomyelitis refractory to conventional treatment is under investigation.

### **Antimicrobial Therapy**

In clinically stable patients suspected of chronic osteomyelitis, bone specimens should be taken prior to initiating antimicrobials, provided that the specimens can be obtained safely in a timely manner. Empirical therapy should be directed against the suspected agents. In patients with vertebral osteomyelitis, antibiotics should be directed towards staphylococci, streptococci, and gram-negative bacilli. Anaerobic coverage should also be considered in patients with osteomyelitis due to pressure ulcers, foot ulcers, oropharyngeal flora, or gastrointestinal pathogens. Both clindamycin and metronidazole have anaerobic coverage and excellent oral as well as parenteral bioavailability.

*Staphylococcus* species are the most common infective agents associated with osteomyelitis and most are no longer sensitive to penicillin treatment (see also

chapter “Staphylococcal and Enterococcal Infections”). Therapy with nafcillin or oxacillin is the therapy of choice for penicillin-resistant but methicillin-sensitive staphylococci. Vancomycin should be considered in patients with penicillin allergies or in osteomyelitis suspected to be due to methicillin-resistant *S. aureus* (MRSA); MRSA is a concern among hospitalized patients, residents of long-term care facilities, and, increasingly, the community. Linezolid is an alternative for resistant gram-positive organisms but may have significant adverse events including bone marrow suppression and peripheral or optic neuropathy (13).

Streptococcal species are typically sensitive to penicillins, and, therefore, penicillin G is recommended. Ceftriaxone is an option for ease of use or for streptococci with intermediate susceptibility to penicillin.

Enteric gram-negative bacilli can be treated with parenteral ceftriaxone as well; however, oral quinolones are noted to have the same bioavailability as parenteral therapy allowing for outpatient treatment in certain situations. Depending on local susceptibility patterns, patients with nosocomial infections such as *Serratia* or *Pseudomonas* should receive antibiotics. Potential agents include: piperacillin-tazobactam, cefepime, ceftazidime, or aminoglycosides. The therapy for osteomyelitis due to mycobacterial or fungal disease is beyond the scope of this chapter (see also chapters “Tuberculosis in Older Adults” and “Fungal Infections”).

Duration of antimicrobial therapy is variable. Acute, uncomplicated osteomyelitis arising from hematogenous spread can be treated with antimicrobials for 4–6 weeks. Chronic osteomyelitis, especially in patients with peripheral vascular disease, may require a longer period of treatment. In order to assess for response or recurrence, inflammatory markers should be monitored intermittently. Occasionally, chronic suppressive therapy with oral agents may be required in patients whose infection can not be controlled by other means.

Elderly patients may be highly sensitive to the potential nephrotoxic effects of certain antibiotics; therefore, such agents should not be used whenever possible. Patients with cognitive issues or unreliable social situations should have therapy in a supervised setting.

## **Surgical Intervention**

The majority of older patients with osteomyelitis may require surgical intervention, as these patients typically present with long-standing infection. Infected bone may require debridement to remove necrotic tissue, sequestra, or abscess. Removal of devitalized tissue and replacement with viable tissue often requires bone or muscle grafting and to allow appropriate healing (3). Surgical treatment may also be required in patients with evidence of spinal instability or cord compression (14). Patients with peripheral vascular disease may need revascularization procedures to prevent limb loss and to improve the likelihood of response to antibiotics. Vascular surgeries are often high-risk surgeries and should be considered carefully in elderly patients with significant comorbidities or functional deficits.

## ***Prevention***

Prevention of osteomyelitis in the elderly begins with optimizing the patient's medical issues. Controlling diabetes, lowering coronary artery disease risk factors, and proper foot care can reduce the risk of osteomyelitis due to peripheral vascular disease. Appropriate dental care, endocarditis prophylaxis, and steps to minimize aspiration risk can prevent transient bacteremia. Avoiding unnecessary use of a condom, indwelling urinary catheters, and intravascular devices will also reduce the risk of infection.

Special care should be taken to prevent pressure ulcers in the bedridden patient by minimizing pressure, friction, shear, and moisture over bony prominences and by also correcting any nutritional deficiencies (see also chapter "Skin and Soft Tissues Infections"). Infection control recommendations for treatment of pressure ulcers should be followed. Pressure ulcers should be routinely monitored for signs of infection. Topical antibiotics, such as silver sulfadiazine, may reduce bacterial counts if superficial infections are found early (15).

Prior to surgeries that involve bone, preoperative prophylactic antibiotics should be given. Patients with acute, open fractures should start prophylactic antibiotics within 6 h of injury.

## **Septic Arthritis**

### ***Epidemiology and Clinical Relevance***

Septic arthritis is of special importance in geriatrics, as it can lead to rapid joint destruction and result in permanent loss of function or even death if not diagnosed and treated promptly. Timely antibiotic and, sometimes, surgical treatment is needed to minimize the loss of cartilage and erosion of subchondral bone that may begin within days of infection. Older age has not only been shown to be a risk factor for septic arthritis but also for poor outcome (16–18). Older adults are more likely to have atypical presentations of bacterial arthritis, because they may have blunted immune responses arising from chronic illness such as diabetes and rheumatoid arthritis, immunosuppressive medications, malnutrition, and cellular and humoral immunity changes associated with aging.

Access to the joint space is necessary for the development of septic arthritis, and, in the vast majority of cases, infection occurs via the hematogenous route. Distant infections in the skin, oral cavity, lungs, heart valves, urinary or gastrointestinal tract often serve as infectious foci. Older adults are prone to skin infections because of aging-related changes to the skin, which lead to skin fragility and delayed wound healing. Less commonly, direct inoculation of the joint may be responsible via animal bites, trauma, orthopedic procedures, arthrocentesis or

intra-articular injections of medications. Finally, direct extension of bacteria from adjacent osteomyelitis can also result in joint infection.

Following entry into the joint space, bacteria adhere to the synovial membrane and proliferate, evoking an inflammatory response, which is due to the combined effects of bacterial products or toxins as well as the host immune response. Increased intra-articular pressure coupled with the release of proteases and cytokines from chondrocytes work to rapidly damage cartilage and subchondral bone.

Older adults are at particular risk for developing septic arthritis, because they often have underlying joint disease such as osteoarthritis, crystalline arthropathy, and rheumatoid arthritis that facilitate the adherence of bacteria as well as the inflammatory process (16). Furthermore, prosthetic joints, intra-articular injections, urinary catheters, and intravascular devices are common in the aging population and increase the risk for septic arthritis.

(NOTE: Prosthetic joint infections will not be discussed in this chapter. Please refer to chapter “Prosthetic Joint Infections in Elderly Patients.”)

### ***Clinical Manifestations***

Typical symptoms of septic arthritis include the acute onset of intense articular or periarticular pain, decreased range of motion, swelling, redness, and warmth. The presence of joint pain and edema are fairly sensitive for diagnosing septic arthritis (17). Older adults with cognitive impairment and an infected joint may not verbalize pain and instead present with subtle changes in behavior. Nongonococcal septic arthritis is usually monoarticular; however, polyarticular involvement can be seen in approximately 10–20% of cases, especially in patients with underlying rheumatoid arthritis (16). The lower extremities account for the majority of infections, with the knee being the most frequently involved (35–50%) followed by the hip (5–15%) (16, 17). Joint effusions are less likely to be observed in septic arthritis affecting small joints such as the interphalangeal joints. Fever occurs in almost half of patients with septic arthritis; its sensitivity in diagnosing nongonococcal bacterial arthritis is only 57% (18). In fact, it has been recommended that if clinical suspicion is high, patients should be evaluated and empirically treated for septic arthritis even in the absence of fevers (19).

### **Specific Types of Septic Arthritis**

Traditionally, bacterial arthritis is divided into nongonococcal and gonococcal etiologies, the latter of which has a better prognosis. Older adults are more likely to present with septic arthritis with nongonococcal infections, because they often have urinary, gastrointestinal, soft tissue and respiratory infections, and they also have catheters and other devices that lead to hematogenous spread of infection to previously damaged joints.



## Staphylococcal and Streptococcal Septic Arthritis

*S. aureus* accounts for the majority of nongonococcal septic arthritis cases, with a prevalence between 40 and 70% of all cases (20). Among these cases, the incidence of MRSA may be increasing and is estimated at 16.6% (21). In addition, there is an exceptionally high propensity for *S. aureus* in patients with septic arthritis and underlying rheumatoid arthritis. As a result, all empirical regimens for septic arthritis should provide adequate coverage for *S. aureus*. Most isolates of *S. epidermidis* from synovial fluid are contaminants, but they can cause bacterial arthritis more commonly following arthroscopy, intra-articular injections of corticosteroids, and other orthopedic procedures. Patients with coagulase-negative staphylococcal joint infections are more likely to present with low-grade fever, normal peripheral leukocyte counts, and mild to moderate joint symptoms.

Streptococcal species are the next most common cause of nongonococcal septic arthritis, accounting for approximately 20% of cases (20). Among these, Streptococcus group A is generally considered the most common isolate and is often associated with skin infections. However, in older adults, Streptococcus group A is rare and groups B, C, and G are predominant (17). Streptococcus groups B, C, F, and G may be associated with conditions often seen in older adults such as diabetes, malignancy, genitourinary, and gastrointestinal infections (21). In patients with malignancies, *Streptococcus pneumoniae* and enterococci are also important causes of septic arthritis.

## Gram-Negative Bacilli

Approximately 10–20% of cases of septic arthritis are due to gram-negative bacillary bacteremia usually from the gastrointestinal or urinary tracts (21). Those at risk for gram-negative infections include elderly patients with comorbid medical conditions, immunocompromised individuals, and intravenous drug users. Older adults are particularly prone to *Escherichia coli* bacterial arthritis because of the propensity to develop urinary tract infections associated with the use of catheters or obstructive uropathy.

## Gonococcal Septic Arthritis

Disseminated gonococcal infection (DGI) may occur in sexually active older adults, and a majority of patients who have DGI also have arthralgias or arthritis as a prominent feature (22). Joint involvement is commonly an asymmetric, transient, migratory polyarthralgia that may resolve spontaneously without joint destruction. However, in approximately 40% of patients, a purulent arthritis can develop that affect the knees, wrists, and ankles. About two-thirds of patients with DGI have discrete painless, nonpruritic small papules, pustules, or vesicles of the extremities and

torso. Two-thirds of patients also develop tenosynovitis of the hands, wrists, ankles, or knees. As 80% of patients will have a positive culture, cultures should be obtained from the endocervix, urethra, rectum, and oropharynx. Synovial and blood cultures should also be obtained; however, these are positive in only about 50% of patients.

### **Unusual Causes**

Nearly any microbial pathogen can cause septic arthritis. Therefore, it is important to pay special attention to clinical clues that may suggest one pathogen over another. For instance, anaerobic bacteria, which cause septic arthritis in 5–7% of cases, should be considered in diabetics, in those with prosthetic joints, in the immunocompromised, and in those with intra-abdominal abscesses or wound infections. If acute joint pain occurs after a dog or cat bite, *Pasteurella multocida* and *Capnocytophaga* spp. infection should be considered. Other rare bacterial pathogens to consider in the appropriate setting would include *Brucella* spp. (ingestion of unpasteurized dairy products), *Borrelia burgdorferi* (tick exposure), *Eikenella corrodens* (human bite), *Streptobacillus moniliformis* (rat bite), and *Mycoplasma hominis* (manipulation of the urinary tract).

### **Differential Diagnosis**

Several noninfectious inflammatory joint diseases can mimic septic arthritis. For instance, patients with acute gout or pseudogout (calcium pyrophosphate dihydrate deposition disease) can also present with fevers, chills, leukocytosis, and monoarthritis that can be difficult to distinguish from septic arthritis. Intra-articular injections of cross-linked hylan into painful osteoarthritic knees may occasionally lead to a severe acute inflammatory reaction that resembles septic arthritis (23). Rheumatic conditions such as rheumatoid arthritis, seronegative spondyloarthropathies, Lyme disease, and mycobacterial and fungal arthritis may present with a painful swollen joint resembling bacterial arthritis. If the older adult with rheumatoid arthritis has one joint that is acutely inflamed, then arthrocentesis should be performed to exclude septic arthritis.

### **Diagnostic Tests**

The definitive diagnosis of septic arthritis ultimately rests on the evaluation of synovial fluid, which should be collected prior to the administration of antibiotics. Synovial fluid should routinely be sent for white cell count with differential, Gram stain, culture, and crystal analysis. In acute bacterial arthritis, synovial fluid is often purulent with white blood cell counts generally exceeding 25,000–50,000 cells/mm<sup>3</sup>,

and often reaching 100,000 cells/mm<sup>3</sup>, with more than 75–90% neutrophils. The likelihood of septic arthritis increases with higher synovial white cell count and with polymorphonuclear cells of at least 90% (18). Gram staining is positive in 50–70% of nongonococcal septic arthritis cases and is less useful in gonococcal arthritis, as it is positive in less than 10% of cases (24). Similarly, synovial fluid cultures are positive in 80–90% of nongonococcal infections; however, they are positive in less than 50% of patients with gonococcal arthritis (22). Gram stain and cultures should always be obtained, even when crystals are seen on wet mount, as crystalline arthropathies and septic arthritis can coexist (25). Culture of synovial tissue may be needed to detect joint infection with Mycobacteria or fungi. Polymerase chain reaction (PCR) techniques have been used to diagnose infections with fastidious or slow-growing bacteria but PCR cannot differentiate between live and dead organisms and is susceptible to contamination (26).

Blood tests can also serve as useful adjuncts in the diagnosis of bacterial arthritis. Blood cultures should routinely be obtained since they are positive in 50% of cases of nongonococcal arthritis, especially in *S. aureus* infections. Serum white blood cell count (WBC), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR), though with high sensitivity and poor specificity, are usually elevated and are helpful in monitoring response to treatment. However, studies have shown that the absence of increased WBC, ESR, or CRP does not exclude the diagnosis of septic arthritis, especially in patients aged 80 or older (17).

Imaging studies may aid the diagnosis of septic arthritis. Plain radiographs are usually normal, but sometimes they may reveal periarticular soft tissue swelling and joint distention. Features of MRI imaging that suggest septic arthritis include the presence of bone erosions and marrow edema, synovial thickening, synovial edema, and soft-tissue edema (27). These features are helpful in diagnosing septic arthritis in the small interphalangeal joints which may not present with effusions. Both MRI and CT imaging are especially useful in detecting effusions in joints that are difficult to examine such as the hip, sternoclavicular, and sacroiliac joints and in determining whether osteomyelitis or periarticular abscesses may also be present.

## ***Treatment***

The management of septic arthritis requires prompt initiation of empirical antibiotics after blood and synovial cultures have been obtained. As mentioned above, early and aggressive treatment is necessary to prevent joint destruction. Unfortunately, there is no prospective evidence that clearly defines the optimal choice and duration of antibiotic treatment. The current standard of practice, while awaiting results of Gram staining and cultures (Table 2), is to select an empirical antibiotic regimen that targets the most likely causative organisms (19). Given the high prevalence of staphylococcal and streptococcal species, all empirical regimens for nongonococcal bacterial arthritis should cover these organisms. In older adults, who may be frail

**Table 2** Suggested empirical antibiotic treatment of suspected native joint septic arthritis (adapted from (19))<sup>a</sup>

Patient group	Antibiotic choice
No risk factors for atypical organisms	Nafcillin/oxacillin 2 g IV q4–6 h or cefazolin 1–2 g IV q8–12 h <sup>b</sup> If penicillin allergic, clindamycin 900 mg IV q8 h
High risk of gram-negative infection (elderly, frail, recurrent UTI, recent abdominal surgery)	3rd generation cephalosporin <sup>c</sup> : Ceftazidime 1–2 g IV q8 h or Ceftriaxone 2 g IV q24 h or Cefotaxime 2 g IV q8 h
MRSA risk (known MRSA, recent inpatient, nursing home resident, leg ulcers or catheters, or other risk factors)	Vancomycin 30 mg/kg IV q12 h plus 3rd generation cephalosporin
Suspected gonococcus or meningococcus	3rd generation cephalosporin <sup>d</sup> : Ceftriaxone 1 g IV q24 h Ceftizoxime 1 g IV q8 h Cefotaxime 1 g IV q8 h
Intravenous drug users	Consult with infectious disease specialist
Intensive care unit patients, known colonization of other organs	Consult with infectious disease specialist

UTI urinary tract infection, IV intravenous, MRSA methicillin-resistant *Staphylococcus aureus*

<sup>a</sup>Antibiotic choice will need to be modified by results from Gram stain and culture

<sup>b</sup>Some recommend vancomycin 30 mg/kg IV q12 due to concerns of community-acquired MRSA. Vancomycin dosing needs to be adjusted based on renal function

<sup>c</sup>If *Pseudomonas aeruginosa* is considered to be a likely pathogen, an anti-pseudomonal cephalosporin such as ceftazidime or cefepime should be given with an aminoglycoside

<sup>d</sup>Empirical treatment for chlamydial infection with doxycycline 100 mg q12 h × 7d or a single dose of azithromycin 1 g should be administered in most cases

and have frequent urinary tract infections, gram-negative coverage with a third-generation cephalosporin administered intravenously (IV) would be appropriate. However, if the older adult resides in a nursing home, has skin wounds, recent catheters, or a known history of MRSA, then the addition of IV vancomycin is indicated. It should be noted, however, that given the rise in community-acquired MRSA, some recommend initial treatment with IV vancomycin even without the presence of risk factors. Though the optimal duration of antibiotic treatment is unclear, patients with septic arthritis are commonly administered IV antibiotics for up to 2 weeks or until symptoms and signs improve, followed by effective oral antibiotics for an additional 4 weeks. In more complex scenarios, such as failure to respond to therapy or infection with unusual organisms, the assistance of an infectious disease specialist is indicated.

A parenteral third-generation cephalosporin is the first-line therapy for DGI in older adults and a switch to oral therapy with cefixime (400 mg every 12 h to complete 7 days of antimicrobial therapy) can be made after symptoms have intramuscular or resolved for at least 24–48 h (28). For patients intolerant to penicillin, intramuscular spectinomycin (2 g every 12 h) can be used. Due to increasing rates of

resistance in the U.S., fluoroquinolones are no longer recommended by the Centers for Disease Control and Prevention for the treatment of gonococcal infections (28). Empirical treatment for *Chlamydia trachomatis* should also be administered, given that 30% of patients are co-infected with this organism. With prompt antimicrobial treatment, the outcome of gonococcal arthritis is favorable and surgical or arthroscopic intervention is seldom required.

Though effective antibiotic therapy is essential to the treatment of septic arthritis, adequate drainage of the infected joint is equally as important and has been associated with improved outcomes (19). The majority of joints can be drained via percutaneous needle aspiration. Repeated, even daily, aspiration may be required. For instance, infected knees may require daily aspiration for up to 7–10 days (29). Serial aspiration can also be used to demonstrate the response to antibiotic treatment, as synovial fluid should become sterile after initial therapy is begun. If the joint is difficult to aspirate, such as with deformed rheumatoid joints or hip, shoulder, or sacroiliac joints, radiologic-guided aspiration, arthroscopy, or open surgical drainage may be necessary. Other situations in which either arthroscopy or open arthrotomy should be considered include the following: the persistence of an effusion beyond 7 days, the development of neuropathy or ischemia resulting from increased intra-articular pressure, the soft-tissue extension of infection, and when less invasive methods of drainage fail (16, 21). Systemic antimicrobial antibiotics are generally continued 1 week after open drainage, with wound healing by secondary intention (16).

During the acute phase, rest and functional splinting are important measures to prevent joint deformity (21). As symptoms improve, early joint mobilization within the first week should be initiated with passive range of motion exercises and can be facilitated with passive motion devices (29). Patients then progress to isometric muscle strengthening exercises and active range of motion exercises to maintain joint function and prevent contractures and muscle atrophy. Traction, dynamic splints, serial casting, or reconstructive procedures may be needed for those patients with residual deformity or limited range of motion from septic arthritis.

Despite improved antibiotics and drainage techniques, the prognosis of septic arthritis remains largely unchanged over the past few decades. Despite the use of antibiotics, mortality rates for in-hospital septic arthritis range from 7 to 15% (18). Increased mortality rates have been associated with host factors such as increased age, coexisting renal or cardiac disease, and immunosuppression (29). The infecting pathogen also plays a part in the prognosis. For instance, *S. aureus* septic arthritis is associated with a higher mortality as compared with that caused by gram-negative bacilli (17). Finally, any delay in appropriate treatment is associated with a worse outcome. This treatment delay is especially pertinent in older patients in whom the time to diagnosis is often longer than that of younger patients because of blunted signs of infection (17).

Septic arthritis also results in significant morbidity. For example, one study found that poor joint outcome, which was defined by the need for amputation, arthrodesis, prosthetic surgery, or severe functional deterioration, occurred in one third of patients (30). Factors associated with poor joint outcome include advanced age, underlying joint disease, and synthetic material within the joint.

## Prevention

Prevention of native joint septic arthritis depends primarily upon addressing predisposing risk factors for bacteremia and direct infections of the joint. In older patients, several preventive strategies should be used such as maximal sterile barrier precautions, chlorhexidine gluconate for insertion of intravascular devices, proper hand hygiene and sterile technique when carrying out procedures, use of catheters impregnated with antimicrobial agents, avoiding unnecessary use of condom and indwelling urinary catheters, optimizing oral hygiene, and prescribing prophylactic antibiotics to prevent endocarditis. In addition, judicious use of immunosuppressive therapies (corticosteroids and chemotherapy), optimizing nutrition, and control of diabetes are also important measures to minimize the risk of developing joint infections.

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# Skin and Soft Tissues Infections

Mira Cantrell and Linda Sohn

## Key Points

- The aging skin and the concept of “skin failure” is discussed.
- Diagnostic evaluations such as blood work and tissue cultures often have limited utility; microbial colonization is common in skin and open wounds.
- Prevention and early recognition of risk factors for the development of pressure ulcers is the key to management.
- There is an alarming increase of the methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), vancomycin-intermediate resistant *S. Aureus* (VISA) strains causing skin infections in the elderly.
- The choice of antibiotics should be based on microbiological data, severity of infection, and clinical status of the patient.

## Skin Structure and Function

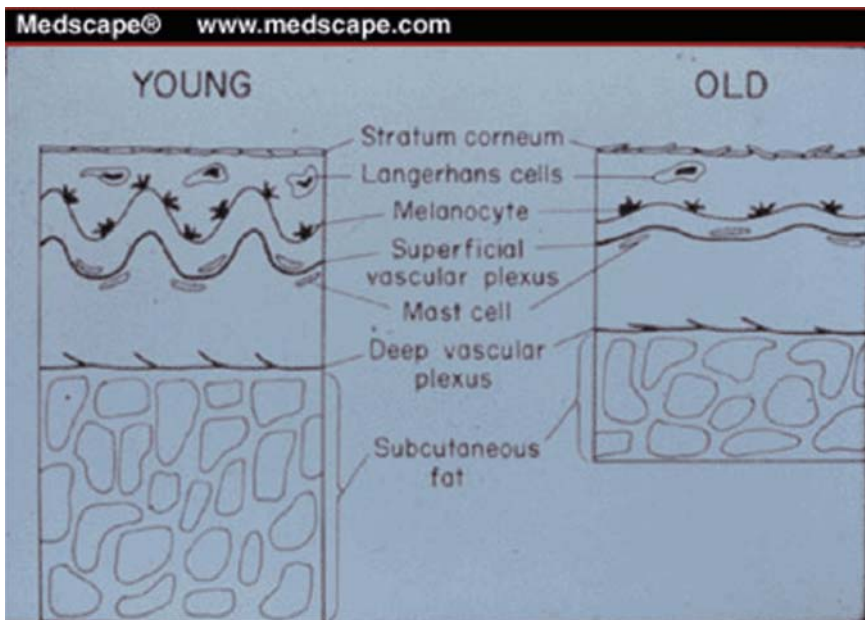
The skin is the largest organ in the body whose integrity protects against microbial invasion, ultraviolet radiation, temperature extremes, and mechanical and chemical trauma. Generally, all strata of the skin, epidermis, dermis, and subcutaneous fat, thin with aging. Changes associated with aging also affect cell replacement, wound healing, immuno-responsiveness, and thermoregulation. In addition to a decreased rate of epidermal turnover, the activity of cutaneous cells also declines: decreased activity of melanocytes, fibroblasts, Langerhans' cells, and sebaceous glands are all presumed due to aging. Consequently, functions such as successful skin barrier, mechanical protection, wound healing, sensory reception, and immuno-regulation

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diminish. Multiple comorbidities such as diabetes mellitus, peripheral vascular disease, and impaired nutrition predispose elderly patients to an even greater degree of skin injury and/or infections. When looking at specific layers of the skin, the loss of integrity and thinning of the dermal–epidermal junction increases the risk of trauma and shear and makes it easier for elderly skin to tear or blister. The dermis contains blood vessels, lymphatics, and nerves; it is composed largely of extracellular matrix such as collagen that give skin its strength and elasticity. Diminished production of fibroblasts in this layer results in decreased production of collagen and elastin; in the elderly, increasing skin fragility contributes to impaired wound healing. Acting as the body’s own natural cushion, subcutaneous fat protects the body from trauma. Reduced amounts of subcutaneous fat result in an impaired ability to diffuse pressure over bony prominences and leads to an increased risk of damage to underlying tissues (Fig. 1). Young adult skin receives one-third of the body’s total blood supply. Vascular aging changes lead to a 60% reduction in basal and peak cutaneous blood supply, especially in the areas with high blood flow. Similarly, the loss and distortion of sensory nerve fibers lead to decreased perception of pain, pressure, and light touch. The number of epidermal Langerhans’ cells (immune cells in skin) decreases by 20–50% and, combined with alterations in the production of interleukins and cytokines, contributes to an overall immunologic decline of aging skin. This leads to delayed healing and increased susceptibility to infections. Superficial lymphatics, located in skin, are less able to maintain normal interstitial fluid levels, leading to edema and interference with normal immune



**Fig. 1** Histologic differences between young and aged skin (1)

system function. Taken together, all these changes help explain the concept of “skin failure” when, due to complex and multifactorial processes, both pathologic and age-related, the skin undergoes a progressive decline predisposing it to insufficient immunologic responses to infectious agents as well as a deficient response to repair of pressure injuries (2). The skin and soft-tissue infections in older adults that are the focus of this chapter are infected pressure ulcers, erysipelas or cellulitis, and necrotizing cellulitis or fasciitis.

## **Infected Pressure Ulcers**

### ***Epidemiology and Clinical Relevance***

It is estimated that prevalence rates for pressure wounds are as high as 24% in the long-term care setting, 38% in acute care, and 17% in home care (3). The treatment of pressure ulcers places an enormous economic burden on the U.S. healthcare system, with direct costs of treatment in the range of \$2.2–3.6 billion annually and with additional costs related to lawsuits affecting both the acute and long-term care settings (4). An estimated 2.5 million pressure ulcers are treated yearly in U.S. acute care facilities with an average cost of \$70,000 for management of a single, full-thickness pressure ulcer. Litigation settlements resulting from the failure to prevent the development of pressure ulcers in long-term care institutions favored long-term care residents and their families in 87% of cases (3). Of great importance is that approximately 60% of pressure ulcers develop in an acute care setting within the first 2 weeks of admission and that 70% of pressure ulcers develop in patients over the age of 70 (5). Therefore, prevention is critical. Not only will the incidence of pressure ulcers be decreased, but also the significant morbidity due to secondary soft tissue and bone infections, worsening immobility, and pain control issues will be avoided.

The risk of developing pressure ulcers increases with the presence of intrinsic factors such as age, immobility, altered level of consciousness, and medical comorbidities, and extrinsic factors such as pressure, friction, moisture, and shearing forces. The prevention of pressure ulcers involves routine skin assessment, management of incontinence/moisture, skin hygiene, and pressure relief either involving repositioning or pressure relief devices; however, if a pressure wound develops a clinician must pay continuous attention to any symptoms and signs that may indicate wound infection.

### ***Clinical Manifestations***

The fundamentals relevant to the wound care of pressure ulcers involve elucidation of cause, proper nutrition, control of infection, and wound management. A thorough clinical assessment is necessary to identify pressure ulcers that have become

infected. Common symptoms and signs such as warmth, erythema, and tenderness may not be present. Increasing size of a wound may be the only clue. In severe cases, bacteremia and osteomyelitis may arise. Osteomyelitis may present as a non-healing wound without systemic symptoms. Bacteremia, due to infected pressure wounds, usually occurs with systemic symptoms such as fever and chills.

### ***Diagnostic Tests***

Diagnostic evaluation of infected pressure wounds is challenging. Because of superficial colonization, cultures of swab specimens of wounds are not clinically diagnostic. Deep tissue biopsies of pressure wounds with other clinical signs of infection are more diagnostically significant. Though bone biopsies are the diagnostic choice for osteomyelitis, this procedure may be too invasive for older adults with more conservative goals of care. Imaging studies can be useful if osteomyelitis is suspected. One study reported sensitivity and specificity of 98% and 89%, respectively, in the usefulness of MRI in the detection of osteomyelitis (6).

### ***Treatment***

Treatment of infected pressure ulcers is controversial, because chronic pressure ulcers are almost always contaminated and/or colonized. When bacterial load reaches the critical mass, defined as  $10^5$  colonies, it will affect the body's ability to heal (5). Newer theories postulate that infected pressure wounds are covered by a numerous mixed-bacterial colonies – a biofilm – that invades the host through the vascular access. A biofilm behaves as an “organism” on its own, producing protective matrices, and is capable of creating the phenotypic and genotypic diversity that provides it with selective adaptation. N/a selective adaptation, in turn, leads to treatment difficulties and failures. Resolution of infection and assistance with wound healing are the ultimate treatment goals. Control of medical comorbidities, for example, elevated blood sugar in diabetes and nutritional supplementation in malnutrition, further aid in wound healing. Local wound care with debridement of necrotic tissue, appropriate dressings, and topical agents are all interventions in wound healing. Topical or systemic antibiotics may need to be administered if infection continues despite aggressive local wound care or with pressure ulcers associated with osteomyelitis or bacteremia. Topical antibiotics might be helpful in reducing the wound bioburden but are not commonly recommended. Oral and parenteral antibiotic selection is based on empirical treatment directed against aerobic and anaerobic pathogens. Since most of the infected pressure ulcers show polymicrobial tissue invasion, antibiotic treatment has to provide broad-spectrum coverage. Monotherapy can be provided by using cefoxitin, ceftizoxime, piperacillin-tazobactam, or imipenem. However, when combination therapy is used, it commonly consists of metronidazole with ciprofloxacin or levofloxacin or clindamycin with ciprofloxacin and levofloxacin.

Widespread colonization with antimicrobial-resistant organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), vancomycin-intermediate resistant *S. aureus* (VISA), and an emergence of multidrug-resistant *Escherichia coli* (*E. coli*) and *Pseudomonas aeruginosa* have all been implicated in treatment failures and/or in the need for extensive and expensive combination antibiotic therapy. Treatment of serious infections with MRSA typically includes vancomycin or the use of newer antibiotics like linezolid and quinupristin/dalfopristin. Milder MRSA infections may be treated with clindamycin, doxycycline or trimethoprim-sulfamethoxazole, depending on sensitivity patterns (see also the chapter “Staphylococcal and Enterococcal Infections”).

## ***Prevention***

As always, effective interventions demand an interdisciplinary team approach and stringent implementation of infection control measures. The infection control program has to establish appropriate infection control practices that will prevent or reduce wound colonization, reduce or eliminate cross-contamination, improve the appropriate use of antibiotics, and train staff in instituting proper prevention and surveillance programs.

## **Erysipelas**

### ***Epidemiology and Clinical Relevance***

Erysipelas, also known as Saint Anthony’s Fire, is an acute streptococcal bacterial infection of the dermis and epidermis often described as a superficial form of cellulitis. It occurs commonly in elderly patients, in those who are immunocompromised, and also in infants and small children. Before antibiotics were commonly used, erysipelas was often fatal. However, even today, patients with predisposing conditions may have recurrent infections or complications, including abscess formation, bacteremia and necrotizing fasciitis (7).

As with other skin infections, disruption of the skin barrier allows for the introduction of the bacterium and, for erysipelas, the offending agent is usually Group A beta-hemolytic *Streptococcus*. Other bacteria such as *Staphylococcus*, *Haemophilus influenzae* and *Klebsiella pneumoniae* have also been implicated (8).

### ***Clinical Manifestations***

Patients typically present with erythematous patches (peau d’orange) that are red, indurated, with defined borders, well demarcated from adjacent uninvolved skin (9). The most common locations are the legs (75–90%) and face (10%), with lesions in

unilateral distribution. The most common portal of entry for leg infections is athlete's foot, while facial erysipelas may develop as a complication of respiratory colonization. The infection spreads rapidly and may involve the lymphatic system with the appearance of enlarged lymph nodes and red streaking of the skin. In severe infections, bullae formation and necrosis may occur. Affected areas are tender to palpation and warm to the touch; additional symptoms such as malaise, fever, and chills may occur.

### ***Diagnostic Tests***

Diagnosis is based on clinical findings. Laboratory tests such as complete blood count and blood cultures may be useful in ruling out other possible diagnosis. Skin cultures are rarely helpful but culture and sensitivity testing of the bullous material – when present – is pathognomonic.

### ***Treatment***

Penicillin is the antibiotic of choice, and it should be prescribed for a 10- to 14-day course. For patients with a penicillin allergy, erythromycin is an alternative. Inpatient treatment is recommended for severe cases, complicated by septicemia, or for immunocompromised patients. Recurrences have been described in some studies to be as high as 20–29%. In patients with a high recurrence rate, continuous antibiotic prophylaxis may be indicated (10).

## **Cellulitis**

### ***Epidemiology, Clinical Relevance and Clinical Manifestations***

Cellulitis is a deeper cutaneous infection that involves skin and soft tissues, often extending into the muscle layer. Unlike erysipelas, it has poorly demarcated borders and – especially in the elderly – may be difficult to distinguish from peripheral edema, deep venous thrombosis, and contact or stasis dermatitis. Portals of entry leading to infection are typically accidental breaks in skin, ulcers, dermatophyte infections, surgical wounds, and burns. While most common sites for cellulitis are lower extremities and digits, it can occur on any part of the body. Cellulitis is most often caused by *Streptococcus pyogenes* and *S. aureus* but, in the elderly, other organisms such as *Pseudomonas* spp., *Serratia* spp., *Proteus mirabilis*, *E. coli*, *Klebsiella* spp., and MRSA need to be included as potential pathogens (11).

## ***Diagnostic Tests***

Diagnosis is made clinically: patients present with a painful, localized area of erythema and edema, occasionally accompanied by regional lymphadenopathy and lymphangitis. Skin swabs are of little or no value, and even needle aspiration and tissue biopsies yield an organism in less than one-third of cases (12). Blood cultures should be done in patients who appear septic, who have significant constitutional symptoms, or who show a sudden functional decline. It should be noted that, as with other types of infections in the geriatric population, fever response may be blunted and leucocytosis may not be present.

## ***Treatment***

Antibiotic treatment of uncomplicated cases is often initiated empirically and should provide both streptococcal and staphylococcal coverage. Agents frequently used and recommended are penicillinase-resistant penicillins, first-generation cephalosporins, erythromycin or tetracycline. If MRSA is suspected, then clindamycin, doxycycline, trimethoprim-sulfamethazole, or daptomycin should be considered depending on local antibiotic sensitivity patterns. In more severe cases, vancomycin, quinupristin/dalfopristin, or linezolid should be prescribed (see also the chapter “Staphylococcal and Enterococcal Infections”). Adjunct treatments like cool compresses, good skin care, pain control, immobilization, and elevation of affected areas are especially beneficial.

## **Necrotizing Fasciitis**

### ***Epidemiology and Clinical Relevance***

Necrotizing fasciitis, commonly known as fasciitis necroticans or “flesh-eating bacteria,” is an infection of the deeper layers of skin and subcutaneous tissue that also involves the fascia within the subcutaneous tissues. “Flesh-eating bacteria” is a misnomer, because bacteria destroy skin and muscle by releasing toxins or virulence factors. Many types of bacteria can cause necrotizing fasciitis, but *S. pyogenes* is the most common cause. Although necrotizing fasciitis is not a common infection, it is associated with high mortality rates. The Centers for Disease Control and Prevention reports that only 500–1,500 cases of necrotizing fasciitis are diagnosed in the United States each year; however, one pooled analysis reported a mortality rate of 34% (13, 14). Risk factors for infection include advanced age, obesity, diabetes mellitus, immunosuppression, peripheral vascular disease, and a history of recent skin trauma/lesion (15).

Early clinical manifestations may include swelling, erythema, and pain, which are symptoms and signs that are also found in cellulitis. Later in the course of the disease, tense edema surrounding the affected area, pain disproportionate to appearance, ecchymosis, blisters, necrosis, and crepitus and/or subcutaneous gas follow in rapid succession (16). A toxic appearing patient with rapid progression of skin changes or a patient with pain out of proportion to the infected skin areas may be further clues in the diagnosis of necrotizing fasciitis. A form of necrotizing fasciitis that occurs in the male genital area is called Fournier's gangrene and may extend to involve scrotum, penis, perineum, and abdominal wall (17).

### ***Diagnostic Tests***

Diagnosing necrotizing fasciitis is difficult. Due to lack of definitive diagnostic tests, a high index of suspicion is needed. Important, however, is the presence of a "necrotizing" component. As with most medical conditions, clinical manifestations, in addition to diagnostic tools, are needed to confirm a diagnosis. Wong et al., developed the LRINEC or laboratory risk indicator for necrotizing fasciitis score, using six widely available laboratory tests to help discriminate between necrotizing and non-necrotizing skin infections (18). The LRINEC also stratifies patients into high, medium, and low risk categories thereby assisting in making emergency care decisions. Aside from laboratory findings, imaging studies are also used in evaluation and diagnosis. Computerized tomography and ultrasound may be useful, but magnetic resonance imaging has been reported to be more sensitive.

### ***Treatment***

Treatment of necrotizing fasciitis involves antibiotics, supportive care, and aggressive debridement. Early and aggressive debridement allows for control of infection and is frequently curative. Since most infections are polymicrobial, broad-spectrum antibiotics are used. Triple antibiotic therapy may be necessary to cover gram-positive, gram-negative, and anaerobic organisms. Regimens frequently used are ampicillin-sulbactam or piperacillin-tazobactam, and ciprofloxacin and clindamycin. Vancomycin should also be added because of the potential presence of MRSA. Antibiotics are continued until no further debridement is needed and the patient is physiologically stable. Other treatment modalities such as hyperbaric oxygen therapy are controversial. In patients with group A streptococcal necrotizing fasciitis, intravenous immune globulin therapy can be beneficial (19). Supportive measures like local wound and skin care, adequate hydration, nutritional support, and stabilization of all other comorbid conditions is of paramount importance in all cases of necrotizing fasciitis.

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# Herpes Zoster

**Kenneth Schmader**

## Key Points

- Herpes zoster is characterized by unilateral, dermatomal pain and rash caused by the reactivation of varicella-zoster virus (VZV) from a latent infection of dorsal sensory or cranial nerve ganglia.
- Aging and cellular immune suppression are the most potent risk factors for herpes zoster.
- The main consideration in the differential diagnosis of herpes zoster is herpes simplex virus reactivation. Patients with recurrent or atypical zosteriform rashes should have definitive microbiological testing (immunofluorescent antibody, culture, or polymerase chain reaction).
- In many older adults with herpes zoster, pain control is the most important objective of treatment; early antiviral therapy and scheduled analgesics help control acute pain.
- The zoster vaccine reduces the incidence of herpes zoster by one-half and the incidence of postherpetic neuralgia by two-thirds.

## Epidemiology and Clinical Relevance

Herpes zoster is caused by the reactivation of varicella-zoster virus (VZV) from a latent infection of dorsal sensory or cranial nerve ganglia (1). Primary VZV infection typically occurs during childhood or adolescence and causes varicella, although immunization with the live attenuated varicella vaccine has altered the natural history of varicella in the United States. Varicella is manifested by a maculopapular and vesicular rash from which VZV enters primary afferent sensory nerves and

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moves to dorsal root ganglia where it establishes a latent infection. During latency, VZV periodically transcribes a limited set of genes and may replicate only to be contained by the cellular immune response. Nearly all older adults in the United States are latently infected with VZV and at risk for herpes zoster.

Aging is the most potent risk factor for herpes zoster (2). Age-related decline in cellular immunity to VZV, which allows for escape of cellular immune containment and “successful” VZV reactivation, appears to be the underlying explanation for the increased risk of herpes zoster with aging. Epidemiological investigations of herpes zoster, in persons of all ages, report incidence rates of 1.2–5.2 cases per 1,000 person years; investigations also document a sharp increase in the likelihood of herpes zoster starting at around 50–60 years of age and increasing into late life in individuals greater than 80 years old (3). The incidence of herpes zoster in persons over 60 years old is 7.2–11.8 cases per 1,000 person years, but nearly all studies used self-report or retrospective medical or administrative record review of clinically diagnosed cases for case detection. The zoster vaccine trial, a VA Cooperative Trial known as the Shingles Prevention Study, was prospective, used active surveillance in a community sample, and diagnosed herpes zoster definitively via VZV DNA detection using polymerase chain reaction (4). In the placebo group of the Shingles Prevention Study, in adults 60 years of age and older, the incidence of zoster was 11.8 cases per 1,000 person years.

The lifetime incidence of herpes zoster is estimated to be 20–30% in the general population and as high as 50% of a cohort surviving to age 85 years old. Each year, the number of cases in the United States is estimated to be about one million with most occurring in older adults (1, 4). With an aging population and the occurrence of immunocompromising diseases (and their therapies) associated with aging, the number of cases of herpes zoster is expected to increase in future decades.

The other potent risk factor for herpes zoster is disease and medication-related suppression of cellular immunity (5). Individuals infected with human immunodeficiency virus (HIV) have much higher incidence rates of herpes zoster (29.4–51.5 per 1,000 person years) than non-HIV infected individuals, and they are at much higher risk for recurrent herpes zoster. Bone marrow and solid organ transplant recipients experience herpes zoster at rates of 5–55% in the first year after transplant. Patients with Hodgkin’s disease, lymphomas, and acute and chronic leukemias are also at a high risk for herpes zoster; other risk factors include white race, psychological stress, and physical trauma.

During the vesicular phase of the rash, a patient with herpes zoster may transmit VZV via direct contact, airborne, or droplet nuclei. If the transmission occurs in a non-immune individual then varicella may result. Persons at risk for varicella include susceptible healthcare workers and staff in hospital or in nursing homes as well as children who have not received the varicella vaccine or who have had an insufficient response to the vaccine. Varicella can cause considerable morbidity in adults, particularly if they are pregnant or immunocompromised. If the herpes zoster rash is only maculopapular or crusted, there is no danger of VZV transmission and subsequent varicella. There is no evidence that exposure of a latently infected individual to herpes zoster causes herpes zoster or varicella.

The most common and dreaded complication of herpes zoster is the development of chronic pain or postherpetic neuralgia. Increasing age is the most potent risk factor for postherpetic neuralgia (6); increasing age is also associated with increased severity of postherpetic neuralgia, so a large majority of persons who suffer from moderate to severe postherpetic neuralgia are older adults. The other major risk factors for postherpetic neuralgia are greater acute pain severity, presence of a prodrome, and greater rash severity (7). The precise incidence and prevalence of postherpetic neuralgia is not clear because of variable definitions and because data on postherpetic neuralgia are not routinely collected and reported in large population groups. Most recent definitions specify any pain 90–120 days after rash onset, which eliminates pain from acute inflammation and ensures a group of patients with true chronic neuropathic pain. By any definition, hundreds of thousands of older adults suffer from postherpetic neuralgia in the United States at any given time.

## Clinical Manifestations

VZV replication and multiplication in the affected dorsal root or cranial nerve ganglion and afferent sensory nerve causes intense neuronal inflammation and damage (1). Early in the process, before the rash appears, older adults commonly experience a prodrome of pain and/or discomfort in the involved dermatome. The pain or discomfort may be intermittent or constant, and it may have aching, burning, itching, tingling, or stabbing qualities. The prodrome may simulate many other painful conditions in older adults, including muscle strain, myocardial infarction, cholecystitis, kidney stones, appendicitis, vertebral compression fracture, and temporal arteritis. The challenge in recognizing prodromal herpes zoster pain may lead to misdiagnosis and misdirected interventions. Clinicians should consider herpes zoster in the differential diagnosis of any acute, unilateral, dermatomal pain syndrome in older adults. It is useful to query for dermatomal neuropathic pain and examine for very sensitive skin in the affected dermatome. The prodrome usually lasts a few to several days, although there are case reports of it lasting weeks to months. A few patients experience acute dermatomal pain without ever developing a herpes zoster rash, a situation known as *zoster sine herpette*.

The diagnosis of herpes zoster usually becomes evident when VZV invades the cells of the dermis and epidermis and causes the characteristic herpes zoster rash. The typical features of the rash include its distribution and appearance. The rash is unilateral and is generally located in the area of skin innervated by a dorsal sensory or cranial nerve ganglion, although lesions in contiguous dermatomes are not uncommon. The most frequently affected dermatomes involve the trunk from T3 to L2 and the ophthalmic division of the trigeminal nerve. The rash begins as red macules and papules in the areas of skin innervated by the anterior, lateral, and/or posterior branches of the sensory nerves. Vesicles usually appear within the first 24 h of rash appearance and may continue to appear for one to several days. The vesicles

tend to dry and crust over in 7–10 days, and the crusts can last for 2–3 weeks, with healing generally occurring by 3–4 weeks. However, the rash is most severe and lasts longest in older people.

Ophthalmic herpes zoster occurs in 10–15% of cases. The rash may occupy any part of the ophthalmic distribution of the trigeminal nerve, but it ends at the midline of the forehead. The location of the rash on the tip and side of the nose is a clue to potential VZV infection of the eye, because this location indicates involvement of the nasociliary branch, which innervates the eye. Potential eye involvement may lead to visual impairment and even blindness from altered corneal sensation, neurotrophic keratitis, uveitis, scleritis, retinitis, choroiditis, or optic neuritis. Herpes zoster may also affect the second and third divisions of the trigeminal nerve as well as other cranial nerves and produce symptoms and lesions in the mouth, ears, pharynx, or larynx. The Ramsay–Hunt syndrome results from involvement of the facial and auditory nerves (facial palsy in combination with herpes zoster of the external ear or tympanic membrane, with or without tinnitus, vertigo, and deafness).

Pain is the principal problem posed by herpes zoster in older adults. The acute neuritis of herpes zoster produces pain that ranges from mild to severe and varies in quality. The pain or discomfort may be described as a deep aching or burning, or sharp and stabbing, or not as pain per se but as tingling, itching, or numbness. For some patients, the pain intensity is so great that words like “horrible” or “excruciating” are used to describe the experience. Acute pain in herpes zoster can significantly decrease quality of life and functional status in older adults. In a prospective, observational study of 160 herpes zoster outpatients age  $\geq 60$ , investigators correlated the Zoster Brief Pain Inventory, a zoster-specific measure of pain and interference with activities, with the Short Form-12 and EuroQOL health-related quality of life measures and activities of daily living (ADLs) questionnaire (8). Herpes zoster pain interfered with all ADLs, but interference was greatest for enjoyment of life, sleep, general activity, leisure activities, getting out of the house, and shopping. Interference with ADLs and reduced health-related quality of life increased significantly as pain severity increased. The impact of acute herpes zoster pain and the importance of pain intensity were carefully demonstrated in a study of 110 patients with herpes zoster using a composite pain measure using four pain ratings (9). Multiple regression analyses showed that the overall pain burden was significantly correlated with poorer physical role and emotional functioning and contributed to decreased role and social functioning. These studies indicate that acute pain in herpes zoster, like postherpetic neuralgia, causes substantial suffering.

In older adults, complications of herpes zoster include the following: secondary bacterial infection of the rash, impaired vision in ophthalmic zoster, stroke secondary to granulomatous arteritis of the internal carotid artery in ophthalmic zoster, focal motor paresis in muscles served by nerve roots of the corresponding affected dermatome, disordered balance, hearing, and facial paresis in cranial neuritis (Ramsay–Hunt syndrome), and meningoencephalitis (10). However, postherpetic neuralgia is the most debilitating complication of herpes zoster. The peripheral and central nervous system damage associated with postherpetic neuralgia negatively impacts health-related quality of life and functional status in older adults, particularly

in patients with moderate to severe pain (i.e., pain score of >3–4 on 0–10 scale). Patients may experience or suffer constant pain (“burning, aching, throbbing”), intermittent pain (“stabbing, shooting”) and stimulus-evoked pain such as allodynia (the experience of pain after a non-painful stimulus such as the touch of clothing). The neuralgia may in turn result in insomnia, depression, physical inactivity, chronic fatigue, weight loss, decreased social activities, and interfere with basic and instrumental activities of daily living. In a vulnerable older adult, severe postherpetic neuralgia may trigger a downward cycle of functional decline that results in loss of independence or death.

## Diagnostic Tests

In the prodromal pain phase, the diagnosis of herpes zoster is not possible, because diagnostic criteria require a rash and current diagnostic technologies can not reliably detect VZV during this phase. However, once the rash appears, a clinical diagnosis is adequate when the typical maculopapular and vesicular appearance and dermatomal location of the rash, coupled with dermatomal pain or discomfort are present. In some individuals, the rash may be only maculopapular and only appear off of the anterior, lateral, or posterior divisions of the sensory afferent nerve that innervates the involved dermatome (i.e., a grouping of red, maculopapular lesions in the anterior chest). In these situations, the diagnosis is challenging and is aided by the presence of a typical neuralgic pain syndrome.

The main consideration in the differential diagnosis of herpes zoster. Herpes simplex commonly recurs many times and usually does not generate chronic pain. However, in some patients, it may be clinically impossible to distinguish herpes zoster from herpes simplex. Contact dermatitis, insect bites, and burns are common conditions that are sometimes confused with herpes zoster. Other less common conditions include the following: papular urticaria, erythema multiforme, drug eruptions, scabies, bullous pemphigoid, pemphigus vulgaris, dermatitis herpetiformis, and epidermolysis bullosa herpetiformis.

Tzanck smears may suggest VZV infection if multinucleated giant cells and intranuclear inclusions are demonstrated in stained vesicle scrapings, but the technique cannot differentiate herpes zoster from herpes simplex virus infections. The definitive diagnosis of herpes zoster requires laboratory evidence of VZV infection either by the isolation of virus in cell cultures inoculated with vesicle fluid, blood, cerebrospinal fluid or infected tissue, or by the direct identification of VZV antigens or nucleic acids in these specimens (Table 1) (11). Laboratory diagnostic testing is particularly useful for differentiating herpes zoster from herpes simplex and for atypical lesions.

Viral culture is the reference standard for diagnosing VZV infection, and the only technique that yields whole VZV for genomic analysis or sensitivity to antiviral drugs. However, VZV is labile so only 30–60% of cultures from proven cases are generally positive. Immunofluorescent staining of cellular material from fresh vesicles or prevesicular lesions can detect VZV significantly more often and faster than

**Table 1** Diagnostic tests for herpes zoster

Test	Characteristics	Comments
Polymerase chain reaction (PCR)	Very high sensitivity and specificity	Fast ( $\geq 1$ day), state-of-the-art technique; useful for crusted lesions
Direct immunofluorescence assay	High sensitivity and specificity	Rapid (3 h), less costly than PCR or viral culture
Viral culture	Low sensitivity, very high specificity	Slower (1–2 weeks), only technique that yields infectious virus for genotype, resistance analyses

virus culture. VZV DNA detection using the polymerase chain reaction (PCR) has the greatest sensitivity, very high specificity, and rapid turn-around time as compared to other techniques and is particularly useful for unusual cases or unusual specimens (e.g., only crusts available for testing). Serologic tests permit the retrospective diagnosis herpes zoster when acute and convalescent sera are available for comparison but are rarely clinically useful.

## Treatment

In older adults with herpes zoster, pain control is the main treatment objective. Pharmacological approaches to zoster pain include antiviral therapy, analgesics, and other supplementary treatments (Table 2) (12). These treatments should be provided in the context of imparting education about the disease to the patient and caregiver and also to dispel myths about herpes zoster. In particular, patients should be told that they will not give shingles to persons who have had prior varicella or who are latently infected with VZV, which is the vast majority of adults in the United States, but that VZV can be transmitted to non-immune individuals if the patient has a vesicular rash.

For older adults who present with herpes zoster within 72 h of rash onset, antiviral therapy is recommended as first-line treatment. Anti-VZV medications licensed for use in the United States include acyclovir, famciclovir, and valacyclovir. These drugs are guanosine analogues that are phosphorylated by viral thymidine kinase and cellular kinases to a triphosphate form that inhibits VZV DNA polymerase and VZV replication. Evidence from randomized controlled trials demonstrate that acute pain and the duration of chronic pain is reduced by oral acyclovir (800 mg five times a day for 7 days), famciclovir (500 mg q8h for 7 days), and valacyclovir (1 g three times a day for 7 days) (1, 12). There are no data to guide clinicians on patients who present more than 72 h from rash onset, but it is not unreasonable to provide antiviral therapy for patients in this situation if they have developed new vesicles in the past 24 h (evidence of ongoing viral replication) or if they have ophthalmic zoster (wider margin of benefit to protect the eye). There are no data indicating that one agent is superior to another, so all three drugs are acceptable agents for older adults. Famciclovir or valacyclovir are generally preferable to

**Table 2** Treatments to reduce acute pain in herpes zoster

Medication	Benefits	Risks	Comments	Oral dosing
Anti-VZV agents:	Reduce acute pain and duration of chronic pain	Nausea, vomiting, headache	Best when used within 72 h of rash onset Accelerates rash healing	Acyclovir: 800 mg five times daily (every 4–5 h) for 7–10 days Famciclovir: 500 mg three times daily (every 8 h) for 7 days Valacyclovir: 1,000 mg three times daily (every 8 h) for 7 days
Non-opioid analgesics	Reduce mild to moderate pain	Hepatotoxicity (acetaminophen) Nausea, vomiting, gastritis, GI ulceration, kidney insufficiency, exacerbate hypertension, congestive heart failure (non-steroidal agents)	Avoid acetaminophen in abnormal hepatic function Avoid or cautious use of NSAIDs in gastritis, peptic ulcer disease, congestive heart failure	Acetaminophen: 650 mg every 4–6 h or 1,000 mg 2–4 times per day NSAIDs – multiple agents, e.g. Ibuprofen 400 mg every 4–6 h
Acetaminophen Non-steroidal anti-inflammatory drugs (NSAIDs)				
Opioid analgesic	Reduce moderate to severe pain	Sedation, nausea, vomiting, dizziness, constipation, pruritis abuse	May not be tolerated by some older adults, particularly frail elders Abuse potential low in older adults with no history of substance abuse	Start with short acting agents (e.g., oxycodone 5 mg every 4–6 h) and titrate; if adequate relief and tolerance, can switch to long-acting agent based on effective 24 h dose of short-acting agent
Corticosteroids	May reduce acute pain; consider use for moderate to severe pain not relieved by antivirals and analgesics	Nausea, vomiting, edema, granulocytosis, hyperglycemia	Does not prevent postherpetic neuralgia or reduce duration of chronic pain	Prednisone 60 mg/day for first week, 30 mg/day for second week, 15 mg/day for third week

VZV varicella-zoster virus; GI gastrointestinal

acyclovir for oral treatment of herpes zoster because of the easier dosing schedule and the higher blood levels of antiviral activity. However, cost and formulary considerations may dictate acyclovir use in some locales. Intravenous acyclovir is indicated in disseminated zoster, central nervous system infection, visceral infection, severe ophthalmic herpes zoster, multidermatomal zoster in the immunocompromised host, and in cases of severe herpes zoster in persons unable to take oral antiviral drugs.

Nausea and/or vomiting, diarrhea, and headache are the most common adverse effects of antiviral therapy and occur in 8–17% of patients. All three antiviral drugs are eliminated through the kidney via glomerular filtration and tubular secretion. Therefore, these drugs must be dose adjusted for kidney insufficiency. Acyclovir is the only drug that has a suspension form for patients who have swallowing difficulties and who cannot tolerate pills.

Pain management principles should be used for managing herpes zoster pain such as scheduled analgesia and use of standardized pain measures such as a 0–10 pain scale. The choice of any analgesic drug must take into account the patient's comorbidities and other medications. Patients with mild-moderate pain may find acetaminophen or nonsteroidal anti-inflammatory drugs sufficient for adequate pain relief. Patients with moderate-severe pain usually need treatment with an opioid analgesic, given that these drugs have demonstrated efficacy for inflammatory and neuropathic pain. A standard approach is to start with a short-acting opioid (e.g., oxycodone, hydrocodone) and monitor the patient's response over time. For patients with ongoing severe pain, the short-acting agent can be switched to a long-acting agent for convenience and more consistent drug levels. For pain flares not covered by long-acting agent, short-acting agents can be used as needed for "rescue." Anticipatory treatment of constipation with stimulant laxative (e.g., senna) is very important when using opioids in older adults.

Despite treatment with antiviral agents and analgesics, some patients will continue to experience moderate to severe pain during the acute phase of the illness, and they will seek additional pain relief. In these situations, clinicians can consider the use of corticosteroids, gabapentin or pregabalin, tricyclic antidepressants, or neural blockade (12).

Randomized controlled trials have shown that corticosteroids do not prevent postherpetic neuralgia and, therefore, are not advocated for routine use in herpes zoster (13). However, several trials with corticosteroids have shown a reduction in acute pain in herpes zoster. In one trial, antiviral therapy and prednisone accelerated time to uninterrupted sleep and return to daily activities in older outpatients with no relative contraindications to corticosteroids such as hypertension, diabetes mellitus, or osteoporosis (14). In addition, herpes zoster patients who develop facial paralysis or cranial polyneuritis may benefit from corticosteroids to reduce pain and to improve motor outcomes. Corticosteroids should always be used concomitantly with antiviral therapy to prevent VZV dissemination. Dyspepsia, nausea, vomiting, edema, and granulocytosis were the most common adverse effects of corticosteroids in herpes zoster clinical trials and use must be carefully weighed against adverse effects in patients with diabetes mellitus, osteoporosis, hypertension, gastritis, among other conditions.



In patients with postherpetic neuralgia, Gabapentin and pregabalin are anticonvulsant agents that have demonstrated efficacy in reducing pain. Convincing data supporting the beneficial effect of these agents on acute pain in herpes zoster or the prevention of postherpetic neuralgia are not available. One study of a single 900 mg dose of gabapentin showed pain reduction over 24 h, and, theoretically, these agents can affect neuropathic pain transmission (15). The adverse effects include dizziness, sedation, ataxia and peripheral edema, which can be particularly problematic in vulnerable adults with cognitive impairment and gait disorders. Although considered off-label prescribing, clinicians are prescribing these agents for acute pain in herpes zoster. If prescribed, small initial doses at bedtime can help with tolerability and also careful titration, depending on the patient's comorbidities, functional status, and other medication. Final dosages of gabapentin and pregabalin will depend on pain relief versus unacceptable adverse effects, assuming there is any effect.

In multiple randomized controlled trials, tricyclic antidepressants have demonstrated efficacy in reducing pain in postherpetic neuralgia. Convincing data on the beneficial effect of these agents on acute pain in herpes zoster or the prevention of postherpetic neuralgia are not available. One small study of amitriptyline or placebo, during acute herpes zoster in older adults, found no effect on pain at 1 or 3 months after rash onset but, at 6 months after rash onset, significantly more amitriptyline recipients were pain (16). The study was limited by the unequal use of acyclovir between the groups and by the use of a potentially hazardous drug (tricyclic antidepressants) in the elderly. Nortriptyline or desipramine are better tolerated in older adults. Small initial doses at bedtime with careful titration and follow-up are recommended. Tricyclic antidepressants may cause cardiac toxicity in patients with a history of cardiovascular disease; an electrocardiogram to screen for cardiac conduction abnormalities must be performed before beginning treatment. Other important adverse effects include dry mouth, constipation, dizziness, orthostatic hypotension, disturbed vision, drowsiness, cognitive impairment, and balance problems. All tricyclic antidepressants must be used cautiously in patients with a history of cardiovascular disease, glaucoma, urinary retention, and autonomic neuropathy.

For patients with pain that is inadequately controlled by antiviral agents, analgesics and supplementary treatments noted above, neural blockade is an important and often unrecognized option. This option requires referral to an anesthesiologist pain specialist. The PINE study, a randomized controlled trial of antiviral and oral analgesics versus antiviral and oral analgesics and a single epidural administration of bupivacaine and methylprednisolone as an outpatient, showed reduction in acute pain but not in the prevention of postherpetic neuralgia (17). More aggressive daily inpatient regimens may reduce acute pain and possibly postherpetic neuralgia.

## Prevention

Given that age-related decline in cellular immunity to VZV is a critical factor in the development of herpes zoster in older adults, investigators tested the hypothesis that boosting VZV-specific immunity in older adults with a zoster vaccine would

decrease the burden of illness due to herpes zoster, the incidence of postherpetic neuralgia, and the incidence of herpes zoster. The Shingles Prevention Study was a randomized, double-blind, placebo-controlled study of the zoster vaccine in 38,546 immunocompetent adults  $\geq 60$  years of age enrolled at 22 study sites across the United States (4) (see also the chapter “Vaccinations”). Subjects were randomized into two age groups (60–69 and  $\geq 70$  years of age), actively followed for HZ, and treated with famciclovir and pain medications if they developed herpes zoster. Herpes zoster was diagnosed in more than 93% of cases by identification of VZV DNA by polymerase in rash specimens; the remainder of the cases were diagnosed by viral culture or independent clinical adjudication. Over the mean of 3.13 years follow-up, fewer than 0.7% of subjects withdrew from study or were lost to follow-up. A total of 957 confirmed cases of herpes zoster (315 among vaccine recipients and 642 among placebo recipients) and 107 cases of postherpetic neuralgia (27 among vaccine recipients and 80 among placebo recipients) were included in the analysis. The zoster vaccine reduced the burden of illness due to herpes zoster by 61.1%, reduced the incidence of postherpetic neuralgia by 66.5%, and reduced the incidence of herpes zoster by 51.3%.

Regarding safety, there were no significant differences between vaccine versus placebo group in deaths (4.1% vs. 4.1%), vaccine-related serious adverse events ( $<0.1\%$  vs.  $<0.1\%$ ), and serious adverse events (1.4% vs. 1.4%) in all 38,546 study participants. A non-random substudy of adverse events using a vaccine report card in about 6,500 individuals showed no difference in rates of hospitalization. Serious adverse events occurred slightly more often in the vaccine group (1.9%) than the placebo group (1.3%). The type of event and frequency of events by body system were not significantly different between groups. Injection site reactions were more frequent in the vaccine group and generally mild. The most common injection site reactions among vaccine recipients were erythema (36%), pain or tenderness (35%), and swelling (26%).

On the basis of this study, the U.S. Food and Drug Administration (FDA) approved live, attenuated zoster vaccine for use in persons 60 years of age and older for the prevention of herpes zoster. The Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) recommends that immunocompetent individuals  $\geq 60$  years of age receive the zoster vaccine to prevent herpes zoster and postherpetic neuralgia. In October 2007, the zoster vaccine was added to the CDC’s Schedule of Recommended Adult Immunizations.

The zoster vaccine should not be used for the treatment of herpes zoster or postherpetic neuralgia, although patients may ask for the vaccine in these situations. The zoster vaccine is contraindicated in individuals with a history of anaphylactic reaction to gelatin, neomycin, or any other vaccine components, individuals who have cellular immunodeficiency diseases (i.e., leukemia, lymphoma, or other malignant neoplasms affecting the bone marrow or lymphoid system, advanced HIV (acquired immunodeficiency syndrome), individuals who are receiving immunosuppressive therapy, including high-dose corticosteroids, and individuals who have active untreated tuberculosis.

The zoster vaccine should be stored frozen at an average temperature of  $-15^{\circ}\text{C}$  ( $5^{\circ}\text{F}$ ) or colder. The zoster vaccine is administered subcutaneously, preferably in the upper arm. It comes in a vial that contains single dose of lyophilized vaccine, which is reconstituted with a diluent. The vaccine should be immediately administered following reconstitution to minimize loss of potency. Because it loses potency rapidly at room temperature, the vaccine should be given within 30 min of reconstitution.

The durability of vaccine response is under investigation. Whether a booster dose will be necessary is unknown at this time. The CDC recommends giving the zoster vaccine to immunocompetent individuals  $\geq 60$  years of age whether or not the patient recalls an episode of varicella, because nearly all older adults in the United States are latently infected with VZV and at risk for herpes zoster. Similarly, the vaccine is recommended for patients who, whether or not, recall a prior episode of shingles, as recurrent episodes of herpes zoster do occur and the shingles history may be inaccurate. A recent well documented episode of herpes zoster will boost VZV-specific cellular immunity significantly, due to wild-type VZV and probably make the use of the zoster vaccine unnecessary.

The live attenuated varicella vaccine was licensed by the FDA in the United States in 1995 to prevent varicella and is on the CDC's Schedule of Recommended Childhood Immunizations (18). The use of the varicella vaccine has led to an estimated 85% reduction in varicella in the United States. The vaccine virus can establish a latent infection and reactivate to cause herpes zoster, but this event appears to develop at a much lower rate than herpes zoster after natural varicella. Whether widespread vaccination of children with the vaccine will significantly reduce herpes zoster incidence in the elderly will not be known until the cohorts of vaccinated children become elderly. However, the vaccine virus is highly attenuated and probably less likely to reactivate and cause complications.

Regarding the potential effect of widespread varicella vaccine use on herpes zoster epidemiology in adults latently infected with VZV, some investigators believe that the reduction in exposure to varicella in adults will reduce exogenous boosting of cellular immunity to VZV and lower the age at which VZV reactivation and herpes zoster occurs. Recent studies of herpes zoster incidence are conflicting as to whether this phenomenon is occurring but it is probably too early to detect a definitive trend.

The prevention of varicella in healthcare workers who care for older adults with herpes zoster in hospital, nursing home or home, is an important issue, particularly in individuals who have emigrated from countries with tropical climates where varicella is less frequent in children and adolescents than in individuals from temperate climates. Healthcare workers who care for older adults should be screened for VZV immunity by first determining if the worker has a history of varicella or shingles. If the worker reports a history of varicella or shingles, then the likelihood is very high that the worker is seropositive and therefore immune. If the worker reports no history of varicella or shingles or are unsure, then he or she should be tested for the presence of VZV antibody. If seropositive, then the worker is immune; if seronegative, then the worker should receive the varicella vaccine. Susceptible

persons should avoid contact with an older adult with herpes zoster until the rash has crusted over. In hospital, the CDC recommends a private room and contact precautions for immunocompetent hospital patients with dermatomal herpes zoster (19). For immunocompromised patients who are hospitalized with localized herpes zoster or any patient with disseminated herpes zoster, the recommendations are a private room with special ventilation and with airborne and contact precautions. In the nursing home, some of these recommendations are not be feasible, but all facilities should use contact precautions for residents for herpes zoster.

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# Orofacial and Odontogenic Infections in the Elderly

Kenneth Shay

## Key Points

- The increasing retention of teeth into advanced age places the present cohort of older people at greater risk for serious dental disease than previous cohorts. With advancing age, older individuals go to the doctor more but to the dentist less. Therefore, physicians caring for older patients need to be aware of common oral diseases in order to suitably advise patients on dental treatment needs and options.
- Dental caries, gingivitis, and periodontitis are infectious diseases, because they are caused by transmissible microorganisms; however, their management is generally directed at reversing or restoring the tissue destruction and reducing the numbers of the responsible organisms rather than eradicating them from the patient.
- Dental and oral pathogens that progress beyond the teeth and periodontium can seed serious infections in both adjacent soft and bony tissues and, via the bloodstream, distant tissues as well.
- Chronic periodontitis is increasingly being implicated as a contributing factor to cardiovascular and cerebrovascular diseases due to the role that elevated, circulating C-reactive protein plays in initiating thrombus formation.
- Periodontal pathogens may cause nosocomial pneumonia. More common respiratory pathogens colonize the oral cavity and, like periodontal pathogens, may be aspirated. Trials directed at reducing nosocomial pneumonia in frail elderly through rigorous oral hygiene regimens have been promising.

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## Epidemiology and Clinical Relevance

The presentation of the oral cavity, and the distribution of diseases that both strike it and stem from it, have changed substantially in the past half-century. The first national study of adult oral health in the United States, reflecting oral health conditions during 1960–1962, reported that 63.5% of Americans over age 75 were fully edentulous (1) (Table 1). In contrast, the National Health and Nutrition Examination Survey III data on oral health from 2004 reported an edentulous rate of 31% for the same age group (2). Put another way, 50 years ago, almost two-thirds of Americans over age 75 had lost all of their teeth, and their dental problems revolved around artificial, tissue-borne replacements. Infectious oral disease in such a population would be predominantly a narrow range of reversible, mucosal fungal infections. The present cohort of elderly Americans has benefited from being exposed to fluoride in drinking water and dentifrice and also by having access to a larger and more sophisticated dental workforce beginning in early adulthood or before. As a result, more than two-thirds of elderly Americans retain some and, in most cases, many of their teeth. The infectious oral diseases encountered in the elderly are therefore now much more likely to be predominantly tooth related: bacterial, virulent, and potentially destructive.

A physician caring for older patients needs to be alert to both the possibility for and appearance of oral diseases and disorders for three reasons. First, the likelihood for destructive oral disease is greater in older patients. The retention of teeth for the full lifespan results in a need to care for the teeth for an entire lifetime. Yet self-care deficits become increasingly prevalent with increasing age, with over 40% of Americans over age 85, and over 85% of residents of long-term care facilities, dependent in at least one activity of daily living (ADL) (3). Toothbrushing is generally regarded as being among the “grooming” tasks grouped among nursing cares such as bathing, which is one of the first ADLs lost as independence declines. Unfortunately, brushing another adult’s teeth is an unfamiliar, distasteful (to both parties) and therefore an infrequent occurrence, even at the hands of nurse aides in

**Table 1** Average number of teeth among U.S. adults with one or more teeth; and percent totally without teeth; by age group, over time

		1960–1962 <sup>a</sup>	1971–1974 <sup>b</sup>	1988–1994 <sup>c</sup>	1999–2004 <sup>c</sup>
55–64	Avg # teeth	17.4	19.5	20.4	22.3
	% edent	36.3	33.2	17.5	10.1
65–74	Avg # teeth	14.8	16.8	19.1	19.3
	% edent	49.4	45.5	28.6	23.8
75+	Avg # teeth	12.3	<sup>d</sup>	16.4	18.4
	% edent	63.5	<sup>d</sup>	40.3	31.3

<sup>a</sup>Johnson et al. (1)

<sup>b</sup>Harvey, C.; Kelly, J. (1981). Decayed, missing, and filled teeth among persons 1–74 years of age. National Center for Health Statistics. *Vital and Health Statistics. Series 11*, No. 223

<sup>c</sup>Dye et al. (2)

<sup>d</sup>Only reported on adults aged 18–74 years of age  
*edent edentulous*

long-term care settings. Likelihood for destructive oral disease is thus greater in the elderly because the behavior generally responsible for minimizing oral disease – daily toothbrushing – is more likely to become impaired with increasing age (4).

Second, many of the medical approaches commonly used to manage disease in those of advanced age reduce the body's own defense against oral disease. Saliva is critical for reducing the oral bacterial and fungal populations through antimicrobial properties and regular swallowing, biochemically neutralizing the caries process, and lubricating tissues to reduce mucosal trauma (5). Yet salivary flow rate and functional properties are highly susceptible to degradation as a side effect of a wide range of medications. Dominant among these are those with anticholinergic properties, which are prescribed for a wide range of conditions, including urinary incontinence, Parkinson's disease, vertigo, depression, anxiety, hypertension, sleep disorders, pain, and nausea (6). Antineoplastic agents are infamous for causing mucositis and ulceration in the rapidly-dividing tissues lining the gastrointestinal tract. Oral ulcerations that become secondarily infected can become life-threatening in the absence of parenteral nutrition.

Third, older people are less likely to receive ongoing dental care with advancing age. The most recent National Health Interview Survey reported that fewer than half of Americans age 65–74 and just 40% of those age 75 and above had seen a dentist in the prior 6 months; 29.3% and 37.4%, respectively, of these age groups reported that it had been 2 years or longer since they had been to a dentist (Table 2). This pattern

**Table 2** Physician and dentist utilization by different adult age groups, 2005. Number of health professional visits per 100 persons per year; and length of time elapsed since last seeing the health professional

Age group	25–44	45–54	55–64	65–74	75–84	85+	
# physician visits/year/100 pt 2003–2004 <sup>a</sup>	242.0	334.8	437.1	605.4	763.4	671.5	
% seeing dentist/year 2005–2006 <sup>b</sup>	61.4	66.2		59.9	57.2	50.5	
Age group		45–64		65–74		75+	
Time since last visit with:		MD <sup>c</sup>	DDS <sup>c</sup>	MD	DDS	MD	DDS
Percent of the age group who last saw the provider within the last 6 months		72.6	50.3	85.5	45.8	88.9	40.8
Percent of the age group who last saw the provider in the interval 6 months–1 year		13.2	16.5	8.7	14.7	6.2	13.8
Percent of the age group who last saw the provider in the interval 1–2 years		6.7	11.6	3.1	9.9	2.9	7.5
Percent of the age group who last saw the provider in the interval 2–5 years		4.2	10.2	1.4	9.6	1.1	10.2
Percent of the age group who last saw the provider over 5 years ago		2.6	11.0	1.0	19.7	0.6	27.2

<sup>a</sup>National Ambulatory Medical Care Survey, National Center for Health Statistics, Trends in Health and Aging. <http://www.cdc.gov/nchs/agingact.htm>. Accessed on 4-27-08

<sup>b</sup>National Health Interview Survey, National Center for Health Statistics, Trends in Health and Aging. <http://www.cdc.gov/nchs/agingact.htm>. Accessed on 4-27-08

<sup>c</sup>Pleis, J.R., Lethbridge-Çejku, M. (2006). Summary health statistics for U.S. adults: National Health Interview Survey, 2005. National Center for Health Statistics. *Vital Health Statistics. Series 10*, 1–153  
MD physician, DDS dentist



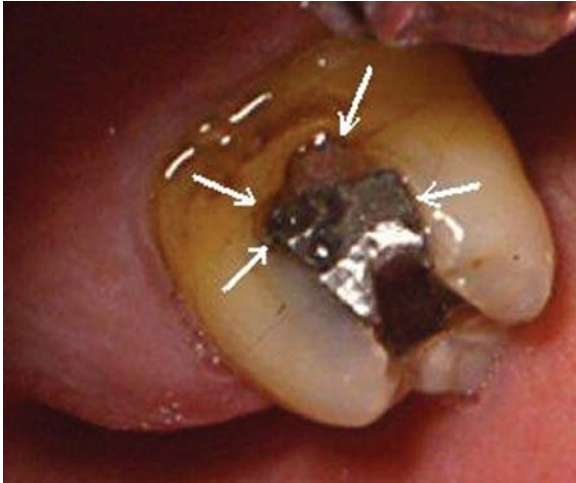
occurs for several reasons. Dentistry is not covered by Medicare. Adult dental benefits under Medicaid are offered in only a minority of states and generally at rates that discourage dentist participation (7). Relatively few individuals carry dental insurance into retirement (8). Dental care is more liable to be regarded as optional by many seniors, most of whose parents were toothless relatively early in adulthood (9). In most cases, dental care is not available to those who are homebound or residing in long-term care facilities. Finally, internal, symptom-based stimuli to seek care (e.g., a toothache or a sensitive tooth) are both less likely (due to age-related reduction in dental sensitivity) and less likely to be perceived as worrisome, as a person ages (10). Yet the National Health Interview Survey demonstrates a steady increase with age into the ninth decade in the number of visits to physicians. As such, physicians have greater likelihood than a dentist to have the opportunity to observe significant, untreated oral pathosis in an older patient. It is therefore important for the physician to be able to recognize such diseases and to have a basic understanding of their pathophysiology and significance in order to offer informed guidance to patients on the health status of this part of their body even though it is customarily the domain of another profession.

## Orofacial Infections

### *Dental Caries*

Dental caries, also called dental decay or cavities, is the visible loss of calcified tooth structure due to dissolution by organic acid secreted by colonies of adherent bacteria. During the first year of life, the bacteria responsible for initiating caries are transmitted from mothers to infants. Nearly 100% of the population has experienced some degree of caries by adulthood. In children and adults in their first six decades, caries generally form wherever bacterial colonies are likely to be relatively undisturbed, which is between the teeth, in the anatomic grooves of the biting surfaces of molars and premolars, adjacent to the gumline, and where improperly-contoured dental restorations irregularly abut natural tooth structure (Fig. 1). With advancing age, root areas of teeth often become increasingly visible and exposed to the oral environment (see below) and “root caries” becomes increasingly prevalent (Fig. 2). For example, only 10.4% of American adults aged 20–34 years in 2005 had experienced root caries, whereas that figure was 42.6% and 49.7%, respectively, for the age groups 65–74 and 75 and older (11).

Dental caries is tracked epidemiologically in several ways. The most common, reflecting the likely history of both treated and untreated caries, is the DMF (Decayed–Missing–Filled) score. The proportion of DMF attributable to “F” (F/DMF) is an index of dental utilization. Studies demonstrate a steady increase in DMF with increasing age to a point and then a leveling, as all susceptible teeth have decayed and have been filled, or been lost. F/DMF is generally lower for lower socioeconomic groups and in very advanced age for all groups.



**Fig. 1** Upper second molar. Recurrent caries forming along the filling/tooth interface (arrows)



**Fig. 2** Root caries

The calcified exteriors of teeth are in a state of chemical equilibrium with saliva. Saliva precipitates a biofilm of proteins on tooth surfaces to which pelagic *Streptococcus mutans* adhere and multiply, forming dental “plaque.” Dietary starches and sugar are metabolized by the bacteria into organic acids that promote dissolution of the calcium phosphate salts (“hydroxyapatite”) of teeth. When sugar and starch are not present, and/or when the bacterial colonies are removed by flossing or brushing, saliva remineralizes the areas of superficial demineralization with salivary calcium. Caries evolves over a period of months if episodes of demineralization in aggregate

remove more tooth structure than is redeposited during periods of remineralization (12). Net demineralization leading to caries comes about when a person frequently consumes sugary or starchy foods (particularly ones that adhere to the teeth, such as caramel or hard candy); fails to regularly remove the bacterial colonies; and/or has reduced salivary flow or impaired salivary anti-caries activity (e.g., as a medication side effect).

The genesis of caries described is essentially the same whether it occurs on the white, enamel-covered surfaces of the teeth or on the roots; however, there is one notable difference. The hydroxyapatite of root mineral is somewhat more soluble in organic acid than the enamel mineral, resulting in more prolonged root dissolution episodes when plaque pH drops. Enamel itself is over 97% hydroxyapatite whereas the hydroxyapatite of root areas is only about 70% of the tissue (the remainder is connective tissue protein such as hyaluronic acid), which means that a given volume of acid can react with a larger volume of root tissue than of enamel tissue (13). As a result of these two factors, root caries proceeds more rapidly than enamel caries.

In its earliest phase, caries can be halted by improved dental hygiene and modified diet. Application of fluoride ion, whether in the form of dentifrice, fluoridated rinse, or brush-on gel (the latter usually dispensed by prescription as a tube of 1.1% NaF gel [preferably] or 0.4% SnF<sub>2</sub> gel), facilitates remineralization (Table 3). The restored hydroxyapatite, now enriched in fluoride, is subsequently less soluble in organic acid. This remineralization process can also occur at a more advanced stage of caries, where a small cavitation (hole) in the tooth surface has formed. But in that more advanced case, the disruption in surface integrity seriously predisposes the tooth to subsequent caries because of the difficulty cleaning plaque out of the cavitation (13).

Dental caries is generally diagnosed post-cavitation, when the treatment needs to be a “filling” – a mechanical debridement of the walls of the cavity and the placement of some insoluble, wear-resistant material that can be contoured to restore the original anatomic form of the tooth. But if the cavitation is not restored, plaque sheltered in the cavitation continues to destroy calcified tissue. The microbiology of established caries lesions evolves to favor more proteolytic forms such as *Lactobacillus* spp., and *Actinomyces* spp. Sometimes undermined tooth structure breaks off whereby the cavitation becomes cleansable, and the caries self-arrests. More commonly, the cavitation proceeds until the neurovascular tissue of the dental pulp is reached and necrosed (with or without symptoms) by bacterial proteases and the host inflammatory response. At this point, the bacteria of the established caries lesion as well as pelagic bacteria of the oral cavity gain access, through the root apex, to the tissues investing the tooth in the alveolus and the circulatory system, which is described below.

## ***Diseases of the Periodontium***

The periodontium consists of a fibrous attachment (“the periodontal ligament”) between the tooth and the cortical bone of the tooth socket and the soft tissues covering the alveolar ridge. Where that tissue is adjacent to the teeth it is termed

**Table 3** Therapeutic interventions for common oral infections

Infection	Rx	Other interventions
Dental caries	For lesions that have not yet disrupted the integrity of the tooth surface, daily application of 1.1% NaF for 6 months has been demonstrated to remineralize over 90% of lesions	Dental restoration Daily application of 1.1% NaF or 0.4% SnF <sub>2</sub> topical gel to all tooth surfaces Twice-daily oral hygiene with a soft-bristle brush and fluoride-containing dentifrice Avoid repeated and/or prolonged exposure to sucrose
Gingivitis	Chlorhexidine gluconate 0.12% oral rinse; 1 oz BID 60 s swish and spit	Dental prophylaxis Twice daily oral hygiene with a soft-bristle brush
Periodontitis	Metronidazole 200 mg tid for 7–10 days following dental debridement OR in conjunction with ciprofloxacin 500 mg each q12h for 8 days following dental debridement.	Dental prophylaxis Subgingival scaling and root planning
Aphthous ulceration	Symptomatic treatment only: Triamcinolone acetonide 0.1% in carboxymethyl cellulose dental paste (“Kenalog in Orabase”)	Identify and avoid causative factors Consider supportive nutrition in severe outbreaks
Candidosis	Fluconazole 100–200 mg followed next day by 50–100 mg daily for 14 days Nystatin oral suspension 100,000 U/mL qid rinse 60 s and spit with dentures out for 7–14 days	If dentures are present, clean daily with commercial soaking agent or 1:10 hypochlorite soak Remove and thoroughly clean dentures hs Investigate possibility for underlying contributing condition, for example, inadequate diabetic control, systemic corticosteroid, broad spectrum antibiotic use, chemotherapy, or medication causing hyposalivation
Herpes simplex	Acyclovir 800 mg 5×/day 7–10 days	Initiate Rx ASAP to minimize severity. Avoid contact with unhealed lesions
Herpes zoster	Acyclovir (as above; if severe and/or ophthalmic involvement, consider IV 10 mg/kg q8h, 7–10 days) or Famciclovir 500 mg q8h for 7–10 days	Initiate Rx ASAP to minimize severity; possibly reduces risk for post-herpetic neuralgia as well Avoid exposure to those without immunity (e.g., infants; immunosuppressed adults) Consider supportive nutrition in severe outbreaks
Dental cellulitis, abscess	Amoxicillin with clavulanic acid, 250–500 mg q8 for 7+ days Clarithromycin 250–500 mg q12 for 7 days	Removal of infection source; incision and drainage

(continued)

**Table 3** (continued)

Infection	Rx	Other interventions
Osteomyelitis	Clindamycin 150–450 mg q6h for 7+ days	Selective removal of necrotic bone. Hyperbaric oxygen
Acute suppurative parotitis	Erythromycin ethylsuccinate 400-800 mg q6h for 7+ days	Provide hydration and intraoral warm saline rinses Reduce use of medications likely to cause hyposalivation

*NaF*, sodium fluoride, *SnF<sub>2</sub>*, Stannous fluoride, *BID* twice/day, *ASAP*, as soon as possible  
*TID* 3 times/day; *QID* 4 times/day



**Fig. 3** Gingivitis, characterized by the hyperemic, inflamed cuff (arrows) of gingival tissue adjacent to the tooth

gingiva. Gingiva is actually attached to the tooth at the most coronal extent (i.e., closest to the biting surfaces) of the periodontal ligament. Further coronally it encases the tooth without being attached to it, forming a virtual space lined by gingiva on one side and tooth on the other. This “gingival sulcus” is 1–3 mm deep if healthy. Extravasated plasma seeps out of this sulcus and nourishes bacterial plaque that flourishes at the tooth–gingiva interface. The plaque is largely composed of cariogenic bacteria and other commensal organisms such as *Prevotella gingivalis*. If the plaque is not regularly removed, plaque metabolites trigger an inflammatory response, gingivitis (Fig. 3). The gingiva becomes edematous and hyperemic, the plasma seeping increases, and the sulcus deepens and may bleed upon brushing. Patients are generally unaware of the condition or note some sensitivity or itching that is seldom severe unless the patient is immunocompromised. Improved brushing (initially causing minor bleeding) will resolve most gingivitis,



**Fig. 4** Gingival hyperplasia, a fibrous, hyperplastic reaction of gingiva to plaque that is so severe as to displace teeth. In the case pictured, the proliferative fibroblastic reaction to dental plaque was triggered by a 7-month-long regimen of felodipine

although an exaggerated, hyperplastic form of the disease that forms in reaction to dental plaque in some individuals taking phenytoin, cyclosporine, or any of the calcium-channel blocking agents, requires surgical excision for resolution (Fig. 4). Resolution of non-hyperplastic gingivitis can also be accelerated by supplementing improved oral hygiene with twice-daily rinsing with mouthwash containing 0.12% chlorhexidine gluconate, triclosan, or an essential oil such as eucalyptol. If the plaque is left undisturbed for more than a day or two, salivary calcium calcifies it, resulting in “tartar” that will require professional removal and which will limit the degree to which the gingivitis can be resolved without professional attention (14).

For reasons still not fully understood but linked to diminished host resistance, the microenvironment at the base of the sulcus may shift to favor proliferation of commensal gram-negative anaerobes such as *Actinomyces actinomycetemcomitans* and *Bacteroides* spp., and fusiforms like *Treponema* spp. An acute inflammatory response (periodontitis) is triggered, lysing periodontal ligament and triggering osteoclastic activity in cortical bone adjacent to the tooth. A deepened sulcus results, which further supports the destructive process by favoring preservation of the protected anaerobic environment (15). The process is invariably asymptomatic, although at more advanced stages, when the sulcus depth has deepened to 5 mm or more, pus may be expressed from the sulcus and marked halitosis results. In advanced periodontitis, spaces open between teeth and the teeth themselves may loosen and in time be exfoliated (Fig. 5).

Periodontitis is largely preventable through meticulous daily oral hygiene. Annual or semiannual professional evaluation can identify early disease onset and initiate therapeutic measures before destruction becomes advanced. Early detection and intervention are particularly important for diabetics who generally exhibit an



**Fig. 5** Periodontitis, characterized by loss of supporting structures (alveolar bone and gingiva) around the teeth



**Fig. 6** Gingival recession, in which part of tooth root is exposed to the oral environment

exaggerated response to periodontal pathogen proliferation (16). Loss of ligamentous and osseous tissue is largely non-reversible, but the process can be stopped by debridement of the sulcus (“root planing”) supplemented by systemic metronidazole or topical formulations of chlorhexidine, tetracycline, or minocycline.

As attachment is lost, the sulcus depth increases unless the opening of the sulcus also migrates in the direction of where the attachment has been lost. Termed gingival recession (Fig. 6), this decrease in sulcus depth leads paradoxically to a periodontally more sustainable status, because a shallow sulcus is less likely to support an

undisturbed pathogenic environment. Unfortunately, gingival recession also puts a tooth at risk for root caries, which can only form when roots are exposed to the oral environment. Recession is more likely to occur if patients receive surgical periodontal treatment, when the rate of attachment loss is slow, when oral hygiene is aggressive, and/or when a tooth or tooth surface is more prominent than its neighbors.

The time course of the loss of periodontal attachment usually follows one of three patterns. One involves progressive destruction of attachment around maxillary incisors and first molars of both jaws and generally is limited to the adult dentition during the second and third decades. A second pattern, which is relatively rare, involves whole-mouth attachment destruction in a matter of several years and is generally due to one of several defects among cellular components of the immune response. The most common pattern is characterized by repeated sequences of a brief episode of inflammation and tissue destruction at an individual site, followed by an extended period of inactivity at that site. Exacerbation episodes occur repeatedly but at varying rates throughout the mouth, and is possibly exacerbated locally, by areas where plaque is more likely to be undisturbed, throughout adulthood. The more gradual loss of attachment is more likely to be accompanied by gingival recession, resulting in the initial and then increasing exposure of root areas to the oral environment. Beginning in the seventh decade and beyond, these destructive cycles become less frequent and severe, likely as a feature of immunosenescence (17).

The progression of periodontitis is generally tracked by assessing the amount of periodontal ligament that has been lost at a given site. Because attachment once lost will not be regained, population reports on periodontal disease severity uniformly reflect increased prevalence and severity with age. This increase is a misleading representation for subjects of advanced age, because such reports reflect not disease activity but prior disease outcome. "Advanced periodontitis" in a person of 70 or 80 years age is likely a stable clinical presentation that merits much more conservative treatment than the same diagnosis given to a patient in his or her 30s or 40s, in which active destruction may still be underway.

Periodontitis is generally more severe among African Americans, Native Americans, and Hispanic Americans. It shows a strong correlation to impaired access to dental services such as lower education and income level and rural residence (18). It is also generally more severe among type II diabetics (16). Although all of these factors are likely to have strong interrelationships, each has been amply established as an independent risk factor.

### ***Mucosal Conditions***

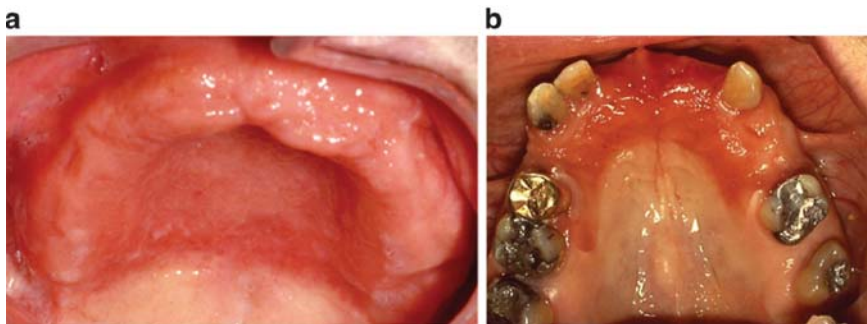
The mucosa of the oral cavity has three distinct conformations, each reflecting its unique functions and each serving as a barrier between the  $10^{11}$ – $10^{12}$  oral microorganisms and the circulatory system. Most of the mouth (e.g., inner aspects of cheeks and lips, tongue ventrum and floor of mouth, soft palate and oropharynx) is



lined by non-keratinized mucous membrane that is dependent on a protective and constantly renewed coating of saliva for hydration and protection from mechanical and bacterial insult. The tongue dorsum is covered by keratinized papilla interspersed by taste pores; it too is dependent on saliva for its function because without regular lavage the taste pores are blocked and the tactile ability of the papilla impaired by buildup of desquamated cells, food debris, and other intraoral flotsam. Finally, the gingiva and the hard palate are covered by a highly keratinized tissue that is relatively immobile against its bony substrate, which protects it from mechanical trauma during chewing.

The most prevalent mucosal diagnosis is, not surprisingly, also the most nonspecific: mucositis. Hallmark characteristics include edema, diffuse inflammatory infiltrate with or without hyperemia, and tactile hypersensitivity. Unless it is due to reaction to fungal metabolites (in which case there is marked hyperemia), mucositis most likely has arisen from cytotoxic chemotherapeutic regimens, therapeutic irradiation, or drug reaction. Treatment should be symptomatic, with attention focused on maintaining adequate nutrition and hydration, and palliation with systemic corticosteroid or corticosteroid and/or analgesic rinses. Need for antimicrobial agents is unlikely unless there is fungal or viral superinfection.

The most common sort of mucositis is a hyperemic variety seen on tissues, most commonly maxillary, covered by a removable denture, and triggered by metabolites of fungal organisms adherent to the prosthesis (19). *Candida albicans* and *C. glabrata* are the organisms most commonly identified. Pelagic forms are non-pathogenic, but when adherent to a substrate such as a denture, colonies form and elaborate irritant metabolites. Intraoral candidosis can present in several forms in addition to mucositis (Fig. 7a, b), including an acute hyperplastic form (“thrush”, characterizes by loosely-adherent, whitish plaques of desquamated cells and fungal colonies on the mucosa (Fig. 8) and a chronic hyperplastic form (“papillary hyperplasia”), in which palatal mucosa proliferates to adopt a characteristically pebbly appearance (Fig. 9). Angular cheilitis is a common candidal lesion of the corners of the mouth (sometimes extending into the nasolabial fold), in which redundant soft



**Fig. 7** Denture stomatitis, also termed chronic atrophic candidosis, in which colonies of fungal organisms residing on an upper denture surface locally irritate adjacent palatal tissue. **a:** typical appearance of denture stomatitis under a complete denture. **b:** appearance under a removable partial denture



**Fig. 8** Thrush, also termed acute hyperplastic candidosis, in which adherent plaques of desquamated cells and fungal organisms adhere loosely to oral mucosa



**Fig. 9** Papillary hyperplasia, also termed chronic hyperplastic candidosis, in which chronic exposure to candidal irritants triggers a proliferative response in the adjacent tissue – in this case, on the mid-palate and on the maxillary alveolar tissue

tissue that accompanies inadequate jaw separation due to inadequately compensated tooth loss ulcerates and bleeds upon wide opening (Fig. 10).

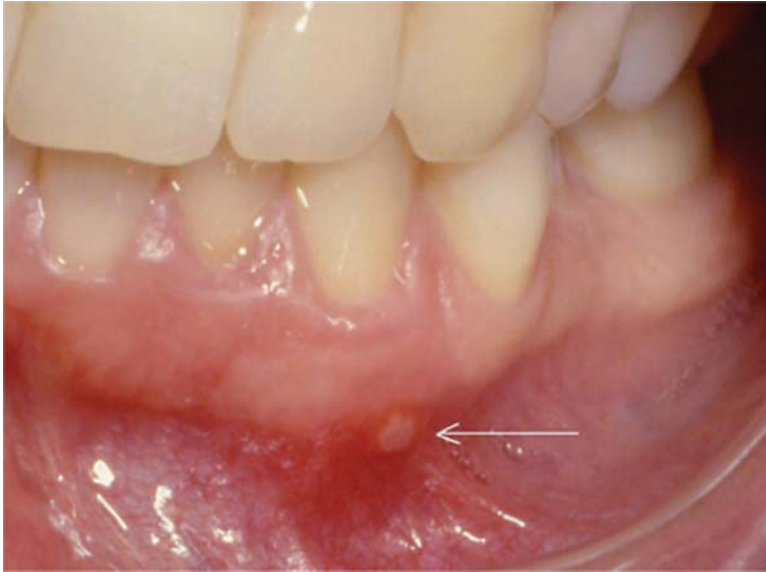
Development and severity of oral candidosis is favored by poor denture hygiene, poorly-fitting dentures, prolonged denture use (e.g., not removing during sleep), drug-induced salivary hyposalivation, elevated blood glucose, and recent use of systemic broad-spectrum antibiotic that suppresses competing microorganisms. Oral candidosis may also indicate an immunosuppressed state (such as human immunodeficiency virus infection or blood cell dyscrasia), which is why its appearance in the absence of other obvious causes should not be dismissed despite the



**Fig. 10** Angular cheilitis, in which the chronically moist state of the corners of the mouth, particularly in situations where the nose and chin have grown closer due to loss of alveolar bony tissue or tooth structure, predispose to infection by fungal organisms

lack of symptoms. Intraoral candidal lesions are readily addressed through four times daily rinsing with nystatin suspension, nystatin or clotrimazole lozenges, or systemic fluconazole. The condition will readily re-emerge, however, unless the underlying cause (e.g., poor denture hygiene, poorly controlled diabetes) is also addressed. Because the methylmethacrylate resin of which dentures are made has a porous surface that shelters candidal colonies from mechanical hygiene practices, brushing a denture only removes gross debris and is not a substitute for chemically-aided cleansing. The dentures of a person with candidosis should be cleaned several times daily with a commercial soak or by immersing in a 1:10 dilution of household bleach for 10–20 min (20).

Because of its relative fragility and rapid cell turnover, non-keratinized oral mucosa is particularly prone to ulceration by a variety of causes. Although most of these are not infectious, the omnipresence of hundreds of microbial varieties makes such physical breaches in the integument highly susceptible to secondary infection. The most common ulcerative condition is aphthous ulcers, also termed aphthous stomatitis or canker sores (Fig. 11). Despite hundreds of studies, the etiology is still unclear, likely reflecting that the same clinical finding – one or more isolated, sensitive elliptical ulcers with yellowish centers and reddish borders, 2–5 mm diameter, appearing on non-keratinized oral tissues – has multiple causes. Often the ulcers are populated with Group A streptococci such as *S. sanguis* or *S. salivarius*, but efforts to implicate these and other organisms as causal have been unsuccessful. Other commonly-invoked causes are physical trauma (such as use of a new toothbrush or following dental care), stressful life episodes, or astringent food (e.g., fresh tomato or



**Fig. 11** Aphthous ulceration, characteristically appearing on parakeratinized mucosa of the mouth

pineapple). Ulcers appear without prodrome and generally clear in 5–7 days without scarring. Most adults experience aphthous ulceration occasionally; when large areas of the oral mucosa are affected and new areas arise as others heal, the condition is termed “major.” Treatment is palliative, consisting of systemic corticosteroid or corticosteroid and/or analgesic rinses. Because lesions are focal, suspension of medication in carboxymethyl cellulose can be applied as an intraoral dressing (21).

The oral cavity and oropharynx are hosts to two fairly common herpetic ulcerations. The more familiar, caused by herpes simplex virus (HSV), is limited to eruptions localized to the highly keratinized mucosa of the gingiva and palate. Clustered and raised circular blisters 1–3 mm diameter form and then burst within 48 h, coalescing into one or more irregular oozing patches that shed live virus particles (Fig. 12). The centers of the patches are yellowish and the patches are surrounded by erythematous haloes. Almost 100% of the populace has experienced a primary herpetic gingivostomatitis due to HSV prior to adulthood and usually without awareness of the infection. The virus subsequently resides in the trigeminal ganglion from which it may periodically cause episodic eruptions, most commonly in the mandibular and sometimes the maxillary distribution of the nerve. Individuals who experience recurrent eruptions often report prodromal symptoms 1–3 days in advance. Administration of acyclovir during the prodromal stage may halt interruption. Once eruption occurs, administration of acyclovir does little or nothing to reduce symptoms or to speed recovery (22).

The second and less common herpetic eruption in the mouths of older persons is due to herpes zoster, also known as “shingles” (see also chapter “Herpes Zoster”). As with HSV, the primary infection by the varicella-zoster virus, or chickenpox,



**Fig. 12** Herpes simplex, characteristically appearing on keratinized mucosa – in this case, the right posterior palate. Very early stage of an outbreak, prior to blister breakage and coalescence of the lesion

generally occurs in childhood, although the introduction of effective vaccines has reduced the proportion of the general population who experiences the primary infection. The virus then resides in a sensory nerve ganglion, most commonly on a single side at the level of one of the lumbar or thoracic vertebrae, from which a re-emergence may later occur, causing clusters of cutaneous, fluid (and virus) filled blisters that burst and form irregular, crusted patches. These heal within a few weeks to leave hyperpigmented, lightly scarred areas that fully resolve more slowly. The distinctive clinical aspect of zoster eruptions is that they are almost always limited to a single side of the midline, and this pattern holds as well when the eruptions are in the distribution of the fifth cranial nerve. Shingles can affect any or more than one of the three trigeminal branches, causing labial, intraoral, and oropharyngeal lesions so painful as to impair food intake and cause lasting loss of oral tissues (23). A further concern with shingles is the emergence of a post-herpetic neuralgia at the site of the eruptions, from which spontaneous pain and/or hyperalgesia can persist indefinitely. Factors favoring the appearance of both shingles and post-herpetic neuralgia are unknown, but a vaccine that effectively reduces the likelihood for both, Zovirax, has recently been approved by Food and Drug Administration (24) (see also chapter “Vaccinations”).

### *Alveolitis*

The bony “alveolar” processes of the mandible and maxilla that hold the teeth are particularly susceptible to infection because they contain the teeth and the surrounding structures. The teeth offer two unique routes through which pathogens can gain

access to the circulation: through a tooth (when its integrity is violated, usually by advanced caries); and through the tooth/socket interface, through the space occupied in health by the periodontal ligament (e.g., as a consequence of advanced periodontitis). When the inflammatory process of a necrotic tooth pulp extends into the cortical bone of the socket and the medullary bone surrounding it, the increased fluid pressure and development of purulent exudate seek an outlet. The outlet may be via the now-empty pulp space of the cavitated tooth or through the gingival sulcus, and among older individuals, the sulcus is the most likely natural history of this process. But the pulp space and the gingival sulcus are very narrow channels and readily become blocked or may be unable to provide adequate drainage. The purulent process in that event extends through the cortical plate surrounding either the maxilla or the mandible and spreads into an adjacent soft tissue space of the mouth, face, or upper neck (Table 4). The resulting cellulitis can be quite dramatic, in a matter of hours significantly distorting the features (e.g., everting the nasolabial fold or closing an eye) or, in the case of a submandibular space cellulitis, compromising the airway by elevating the floor of the mouth or (in the case of an extension into the retropharyngeal space) constricting the pharynx. The rapidity and severity of the cellulitis is usually such that immediate incision and drainage is indicated, the exudate is cultured for sensitivity, and parenteral antibiotic is initiated. Generally 24 h of drainage plus antibiotic therapy resolves local conditions to the point that local anesthesia becomes effective. Removal of the offending tooth (the major source of infection) provides additional drainage. Pathogens cultured from cellulitis of dentoalveolar origin are generally not either typical caries- or periodontitis-causing organisms but are agents resident in the mouth that become established in the environment of the necrotic dental pulp, such as *Actinomyces viscosus*, *Staphylococcus aureus*, or *Streptococcus pyogenes*.

Odontogenic infection has the potential to also infect the bone. Osteomyelitis affecting the maxilla or, more commonly, the mandible is a risk of acute and especially chronic infection among older diabetics and others of advanced age who have impaired ability to fight infection. Osteomyelitis is diagnosed by a combination of history, characteristic (“cotton-wool”) radiological appearance, and biopsy. Management in most cases can be accomplished through a combination of debridement and parenteral antibiotics. In severe cases, and those complicated by avascular bone, hyperbaric oxygen treatments offer significant benefit (25).

In people of advanced age there are two predisposing conditions to odontogenic osteomyelitis that merit mention. Osteoradionecrosis (ORN) is a condition of diminished vascularity and cellularity of bone resulting from exposure to ionizing radiation administered as a component of cancer therapy. Bone in the radiation beam remains vital but has markedly diminished turnover and, therefore, impaired healing ability. Removal of a tooth from irradiated bone substantially increases the likelihood for post-extraction osteomyelitis, particularly if the tooth was in the mandibular arch. The avascular nature of irradiated bone makes pre-extraction and post-extraction hyperbaric oxygen advisable (26).

Expanding use of bisphosphonate agents to manage bony metastasis (commonly from a prostate primary) and multiple myeloma through osteoblast suppression has resulted in a profusion of reports of oral osteomyelitis induced by dental trauma among patients who have received repeated infusions of the amine-containing

**Table 4** Comparative features of odontogenic deep fascial space infections of the head and neck

Space infections	Usual site of origin	Pain	Trismus	Swelling	Clinical Features	
					Dysphagia	Dyspnea
Masticator						
Masseteric and pterygoid	Molars (especially third)	Present	Prominent	May not be evident (deep)	Absent	Absent
Temporal	Posterior maxillary molars	Present	None	Face, orbit (late)	Absent	Absent
Buccal	Bicuspid, molars	Minimal	Minimal	Cheek (marked)	Absent	Absent
Canine	Maxillary canines, incisors	Moderate	None	Upper lip, canine fossa	Absent	Absent
Infratemporal	Posterior maxillary molars	Present	None	Face, orbit (late)	Occasional	Occasional
Submental	Mandibular incisors	Moderate	None	Chin (firm)	Absent	Absent
Parotid	Masseteric spaces	Intense	None	Angle of jaw (marked)	Absent	Absent
Submandibular	Second, third mandibular molars	Present	Minimal	Submandibular	Absent	Absent
Sublingual	Mandibular incisors	Present	Minimal	Floor of mouth (tender)	Present if bilateral	Present if bilateral
Lateral pharyngeal						
Anterior	Masticator spaces, occasional	Intense	Prominent	Angle of jaw	Present	Occasional
Posterior	Masticator spaces, severe	Minimal	Minimal	Posterior pharynx	Present	Severe
Retropharyngeal (and danger)	Lateral pharyngeal space, distant via lymphatics	Present	Minimal	Posterior pharynx (mid-line)	Present	Present
Pretracheal	Retropharyngeal space, anterior esophagus	Present	None	Hypopharynx	Present	Severe

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variants zoledronic acid and pamidronate. Isolated case reports have also implicated oral agents administered for osteoporosis such as alendronate and risedronate. Epidemiological analysis has been (fortunately) impaired by small case numbers, but meta-analyses of published reports suggest that the parenterally-administered aminobisphosphonates are far more likely to contribute to an osteonecrosis of the jaw (ONJ); the mandible is much more susceptible than the maxilla; and women are more susceptible than men. There are conflicting conclusions as to whether total dose is correlated with increasing risk, and no data suggest diminished chance for ONJ results from suspension of ongoing bisphosphonate administration. On the basis of data currently available, the dominant conclusions are that the risk for ONJ is eclipsed by the benefits of oral therapy for osteoporosis; all dental professionals need to be alert to the increased likelihood for this complication to oral trauma represented by prior or current use of bisphosphonate. Patients contemplating bisphosphonate therapy and, particularly those under consideration for irradiation of the head and neck, are strongly encouraged to first address known and likely dental surgical needs in advance of either a ONJ- or ORN-inducing regimen (27, 28).

### ***Oropharyngeal Adenitis and Parotitis***

Glandular tissues relevant to the mouth and oropharynx include the major salivary glands (parotid, submandibular, and sublingual) and the minor salivary glands of the lips, cheeks, and palate. Actual infections of the minor salivary glands are uncommon, although non-infectious, mechanical ductal blockage can result in a painful mucocele that is readily resolved by incision or gland excision (Fig. 13).



**Fig. 13** Mucocele: a blocked minor salivary gland of the lower lip – usually an aseptic process – continues to excrete its mucinous product, potentially causing pain as tissues are displaced



The major glands may become blocked due to salivary stones. This non-septic but uncomfortable condition generally can be resolved non-surgically by manipulation and retrieval of the blockage through the duct. The most common infection of these structures is viral parotitis or mumps, which is generally a disease of childhood that occasionally occurs in adults, even elderly ones, particularly males. Among debilitated elderly, a relatively rare but still concerning infection is bacterial parotitis, usually brought about when severe hyposalivation permits ingress of oral pathogens into the gland through the parotid duct. Patients are febrile, often significantly dehydrated (more as a contributing cause than an outcome), have unilateral preauricular tenderness and swelling, and pus can often be expressed from the parotid duct. Parenteral antibiotic and fluids should be initiated, the exudate cultured, and frequent warm saline rinses encouraged to promote ductal drainage. A review and adjustment of the patient's medication regimen to minimize or eliminate use of xerogenic agents is strongly indicated (29).

## **Metastatic Odontogenic Infection**

The large number of pathogens in the highly vascular and disease-prone oral cavity logically suggests that there would be threats of oral origin to the rest of the body, but the strength of data supporting such threats is variable and still evolving. The three classes of purported impact of oral infections on other parts of the body are blood-borne pathogens seeding infection of distant organs and implants, oral pathogens seeding nosocomial pneumonia through aspiration, and the systemic impact of inflammatory mediators resulting from orofacial infection.

### ***Infection Due to Blood-Borne Pathogens***

During the early twentieth century, the discoveries about the bacterial origins of disease by Lister and Pasteur set the stage for widespread allegations in the medical and the dental literature that untreated dental disease (notably gingivitis and periodontitis) was responsible for a range of poorly-understood, chronic conditions such as gastroenteritis and arthritis (30). Although little to no data backed up these purported relationships, it is unconfirmed, but widespread lore, that as a result numerous individuals had all of their teeth removed to address non-oral maladies.

In the 1930s, microbiological studies confirmed that bacteremia of multiple oral pathogens was a consequence of dental surgery. Subsequent work demonstrated that oral hygiene and chewing in the presence of periodontal disease also caused bacteremia (31, 32). In the latter half of the century, case reports have appeared of infections of the liver, kidney, brain, and bone by pathogens generally not found outside the oropharyngeal region (33). These reports generally identify the causative

organism and include history of odontogenic infection with or without treatment at a time proximate to the organ infection. Identification of the pathogen(s) of the odontogenic infection itself is seldom provided. The rarity of such occurrences leads to their being reported in the literature but also suggests how infrequently they occur. There was and is no basis for believing them any more or less unusual with advancing age.

Bacterial endocarditis (BE), however, has a much more robust case for presenting a tangible risk of odontogenic origin. The viridans group streptococci is the causative organism in approximately one-third of the cases of BE, and this organism is normally present primarily in the mouth (34). Disrupted flow past cardiac valves offers conditions favorable for bacterial adherence and colonization, which is why a history of rheumatic heart disease, a prior history of BE, an artificial mitral or tricuspid valve, or a congenital valvular malformation is associated with increased risk. Committees of the American Heart Association have regularly issued position statements since the 1960s identifying those at elevated risk for BE and articulating preventive regimens designed to minimize cardiac consequence of streptococcal bacteremia. These reports have been updated as new data become available. The most recent set of recommendations (Table 5) attributes the lack of evidence for reducing BE through prophylactic antibiotic to the frequent occurrence of bacteremia due to routine daily function. In light of the demonstrated risks of widespread antibiotic use (e.g., anaphylactic allergic reaction, emergence of resistant organisms), the latest recommendations are that only those at highest risk for BE (i.e., those with prosthetic valves and a prior history of BE) should be covered for dental procedures; all patients at increased risk for BE should be encouraged to maintain high levels of oral health (34) (see also Chapter "Infective Endocarditis").

Also receiving attention for elevated risk for odontogenic metastatic infection are artificial implants, including pacemakers and defibrillators, intravascular stents, vascular and cerebrospinal fluid shunts, breast implants, and penile and joint prostheses (35). The American Heart Association standards have long specifically excluded pacemakers, and, more recently, implanted defibrillators from their list of indications for prophylactic antibiotic coverage for dentally-induced bacteremia. A limited literature offers a loose consensus that intravascular stents and grafts endothelialize in a matter of days or weeks, supporting the general recommendations that no prophylactic coverage is needed after 6 weeks for small devices like coronary artery stents, or after 6 months for larger repairs such as aortic and other large-vessel aneurysm grafts. There are no published recommendations regarding arterio-venous shunts for dialysis or for ventroperitoneal shunts placed to manage hydrocephalus. No evidence-based recommendations have proliferated concerning precautions for patients with vena cava or other large-vein intraluminal filters placed to mitigate potential consequences of thromboembolism. Little to no literature exists on the risk posed by penile or breast implants. Despite the absence of evidence-based recommendations, many physicians nevertheless suggest or insist on empirical prophylactic regimens for patients with these devices who are about to undergo dental procedures.

**Table 5** Prevention of infective endocarditis in elderly dental patients; after Wilson, et al. (34)

Cardiac conditions for which:	Dental treatments for which:	Standard antibiotic prophylaxis regimen
Prophylaxis IS recommended: Prosthetic cardiac valves or prosthetic material used for cardiac valve repair Prior history of infective endocarditis	Prophylaxis IS recommended: For all dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of oral mucosa, such as: <ul style="list-style-type: none"> <li>Dental extractions</li> <li>Periodontal procedures, including surgery, root planning, scaling, and probing</li> </ul>	Standard regimen: <ul style="list-style-type: none"> <li>Amoxicillin – 2.0 g po 1 h before procedure</li> </ul> Unable to take oral medications: <ul style="list-style-type: none"> <li>Ampicillin – 2.0 g IM or IV</li> </ul> OR <ul style="list-style-type: none"> <li>Cefazolin or ceftriaxone – 1.0 g IM or IV 30 min before procedure</li> </ul>
Congenital heart disease (CHD) limited to: <ul style="list-style-type: none"> <li>Unrepaired cyanotic CHD, including palliative shunts and conduits;</li> <li>Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or catheter intervention, during the first 6 months after the procedure; and</li> </ul>	<ul style="list-style-type: none"> <li>Dental implant placement and reimplantation of avulsed teeth</li> <li>Endodontic (root canal) treatment in which an instrument extends beyond the tooth apex</li> <li>Subgingival placement of antibiotic fibers or strips</li> <li>Subgingival rubber dam clamp placement</li> </ul>	Allergic to amoxicillin: <ul style="list-style-type: none"> <li>Clindamycin 600 mg orally 1 h before procedure</li> </ul> OR <ul style="list-style-type: none"> <li>Cephalexin<sup>a</sup> or other first- or second-generation oral cephalosporin in equivalent dose, 2.0 g 1 h before procedure</li> </ul> OR <ul style="list-style-type: none"> <li>Azithromycin or clarithromycin, 500 mg 1 h before procedure</li> </ul>
<ul style="list-style-type: none"> <li>Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device</li> </ul>	<ul style="list-style-type: none"> <li>Initial placement of orthodontic bands but not brackets</li> <li>Intraligamentary local anesthetic injections;</li> <li>Prophylactic cleaning of teeth or implants where bleeding is expected.</li> </ul>	Allergic to penicillin and unable to take oral medications: <ul style="list-style-type: none"> <li>Clindamycin 600 IV within 30 min before procedure</li> </ul> OR <ul style="list-style-type: none"> <li>Cefazolin or ceftriaxone<sup>a</sup> 1.0 g IM or IV within 30 min before procedure</li> </ul>
Cardiac transplantation recipients who develop cardiac valvulopathy		

<p>Prophylaxis is NOT recommended for: Any form of CHD other than listed above.</p>	<p>Prophylaxis is NOT recommended for: Restorative dentistry (without intrasulcular retraction cord)</p>
<p>Previous coronary artery bypass graft surgery or stent</p>	<p>Local anesthetic injections through non-infected tissues (non-ligamentary)</p>
<p>Mitral valve prolapse with or without valvular regurgitation</p>	<p>Placement or adjustment of removable prosthodontic or orthodontic appliances</p>
<p>Physiologic, functional, or innocent heart murmurs</p>	<p>Bleeding from trauma to the lips or oral mucosa</p>
<p>Previous rheumatic fever without valvular dysfunction</p>	<p>Postoperative suture removal</p>
<p>Cardiac pacemakers and implanted defibrillators</p>	<p>Making impressions Intraoral radiography</p>
<p><sup>a</sup>should not be used in patients with immediate-type hypersensitivity reaction to penicillins <i>IM</i>, intramuscular; <i>IV</i>, intravenous</p>	

There is a considerable literature of case reports, recommendations, and analyses for risks and benefits associated with odontogenic bacteremia and joint prostheses. The most numerous and credible of these publications concern total hip arthroplasty (THR), where approximately 7 cases in 10,000 fail 6 months or later after placement (36). The temporal proximity of such failures to odontogenic infection, plus the fact that a number of the microbial species recovered from infected, failed prostheses may be found in the oral cavity, resulted in an empirical recommendation by many orthopedists for lifetime antibiotic prophylactic coverage prior to dental procedures likely to cause bacteremia. However, a recent joint publication by the dental, orthopedic, and infectious diseases communities (37) has meticulously evaluated the relevant literature and made the recommendation that pre-dental prophylaxis is only indicated under a limited set of circumstances: hip prostheses under 2 years old, prostheses previously infected, immunocompromised patients, and patients with either rheumatoid arthritis or insulin-dependent diabetes. The recommendations noted that inadequate information exists on which to draw conclusions about other joints (e.g., knee, shoulder, toe) or other implanted devices.

### ***Oral Pathogens Seeding Nosocomial Pneumonia Through Aspiration***

Nosocomial pneumonia is seeded by pathogens, most frequently gram-negative anaerobes, residing in the oral cavity. Nosocomial pneumonia is the leading cause of death and the leading reason for hospitalization among nursing home residents as well as being the second most common infection reported for this group. A “perfect storm” of risk factors for nosocomial pneumonia both characterizes this group and predisposes it to acquiring pneumonia: limited or no physical activity, high rates of aspiration, hyposalivation, poor oral hygiene, dependent in feeding, untreated dental disease, high salivary counts of caries and periodontal pathogens (which are dominantly gram-negative anaerobes), and an environment infamous for outbreaks of transmissible infectious diseases. Periodontal pathogens themselves have been implicated in nosocomial pneumonias and sequential intraoral sampling of patients in health care institutions reveals that rapidly rising rates of gingival and oropharyngeal colonization by pulmonary pathogens accompany increasing lengths of stay (38).

Clinical trials in the literature demonstrate that oropharyngeal cleaning in nursing home residents and intensive care unit patients reduces nosocomial pneumonia incidence, severity, and outcomes. Regimens trialed have included daily chlorhexidine gluconate 0.12% rinse, daily povidone–iodine swab, daily toothbrushing by nursing staff, and regular dental prophylaxis by a dental professional. A recent meta-analysis concluded that there was good evidence (1, grade A recommendation) that improved oral hygiene and frequent professional oral health care reduces the progression or occurrence of respiratory disease among high-risk elderly adults living in these two populations (39).

## ***Systemic Impact of Inflammatory Mediators Resulting from Orofacial Infection***

Chronic periodontal disease leads to elevation of C-reactive protein (CRP) in circulating blood. It has been established epidemiologically that poor periodontal health is correlated with impaired glucose control in diabetics (16). The evidence associating elevated CRP in pregnant women to low birth weight (40) is sufficiently strong that many medical insurers now cover dental prophylaxis as part of a pre-term obstetric benefit. Elevated CRP also favors thrombus formation (41). Mattila and colleagues (42) reported in 1989 a correlation between periodontal and cerebrovascular diseases, and that relationship has been refined and strengthened since by several other centers. There is some evidence that periodontal therapy reduces CRP levels (43). Yet evidence still does not support undertaking dental care as a means for reducing the risk for cerebrovascular disease (44).

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# Ocular Infections

Gary N. Holland

## Key Points

- In older patients, the prevalence of many ocular infections is increased.
- Increased risk of infection is due to multiple factors (described herein) that are amenable to intervention.
- In older patients, the severity of ocular infections, when they occur, can be greater than those of younger patients.
- Response to treatment may be poor in elderly patients, necessitating more aggressive or prolonged treatment.
- Older patients may have problems self-administering topical treatment effectively.

## Introduction

Elderly individuals may develop a variety of ocular infections, involving the adnexae, the ocular surface, or the intraocular tissues. None are unique to older patients, but some (not all) are more prevalent among the elderly, and many are substantially more severe in this population. There are a variety of reasons for these associations, which include the following:

- Anatomic factors that compromise natural defenses on the ocular surface
- Social factors (e.g., confinement to a nursing facility) that increase exposure to pathogens
- Situational factors such as medical care (surgery, intravenous catheters) that facilitate infection with ubiquitous organisms
- Waning of immune defenses in older patients
- Mental and physical changes that alter a person's ability to prevent infection or to treat infections effectively

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“Natural defenses” are critical for protection of the ocular surface from infectious agents; they include normal eyelid function, an adequate tear film, and an intact conjunctival and corneal epithelium. Increased exposure of the ocular surface can lead to drying and to a breakdown of the corneal epithelium. Exposure can result from a variety of eyelid problems, including inability to close the eyelids (Bell palsy, excessive tissue removal during blepharoplasty) or ectropion formation (out-turning of the lower eyelid; either cicatricial or involuntional). Eyelid dysfunction can also interfere with maintenance of a normal tear film and with flushing of tears and contaminants through the nasolacrimal drainage system. A normal tear film is critical for maintaining the health of the corneal epithelium. Decreased tear production occurs with aging (1), and severe dryness can lead to a breakdown of the intact corneal epithelium. Eyelid laxity, without obvious ectropion, can also compromise the ocular surface through lack of normal eyelid function that causes stagnation of the tear lake. Entropion (in-turning of the eyelid) can compromise the ocular surface because of trichiasis (rubbing of the eyelashes on the cornea).

Intraocular infections can either be exogenous, as a result of penetrating trauma or as a complication of surgery, or they can be endogenous, the result of hematogenous spread from non-ocular sites of infection. Hematogenous seeding can also be associated with infected catheters or other invasive procedures. The prevalence of such infections is higher in older patients, which can be attributed to the increased frequency with which they undergo surgery and with which they develop serious medical conditions associated with non-ocular infections.

Mental and physical changes associated with aging can limit a patient’s capacity to prevent infection, can cause a delay in diagnosis of infection, and can limit a patient’s ability to manage an infection appropriately in its early stages. Poor hygiene, for example, can result in blepharitis (inflammation of the eyelids), with an overgrowth of bacteria on the eyelid margins, or contamination of topical medications. Arthritis can prevent the proper instillation of such medications.

Described below are five ocular infections or categories of infections that demonstrate the spectrum and diversity of disorders that can occur in older patients and illustrate influences on the prevalence and severity of disease. They include ocular surface and adnexal infections (bacterial conjunctivitis, corneal ulcers), herpetic eye diseases, including herpes zoster ophthalmicus and herpes simplex virus (HSV) keratitis, exogenous endophthalmitis, endogenous infections of the choroid and retina (candidal chorioretinitis, endogenous bacterial retinitis, necrotizing herpetic retinopathies such as the acute retinal necrosis (ARN) syndrome), and ocular toxoplasmosis.

## **Adnexal and Ocular Surface Infections**

As with other areas of skin, it is normal for the eyelid margins to be colonized by bacteria, and these bacteria are a major source of ophthalmic infections. Blepharitis, which is often associated with inflammation of the meibomian glands at the base of the eyelashes (meibomitis), can result in an overgrowth of bacteria, thereby

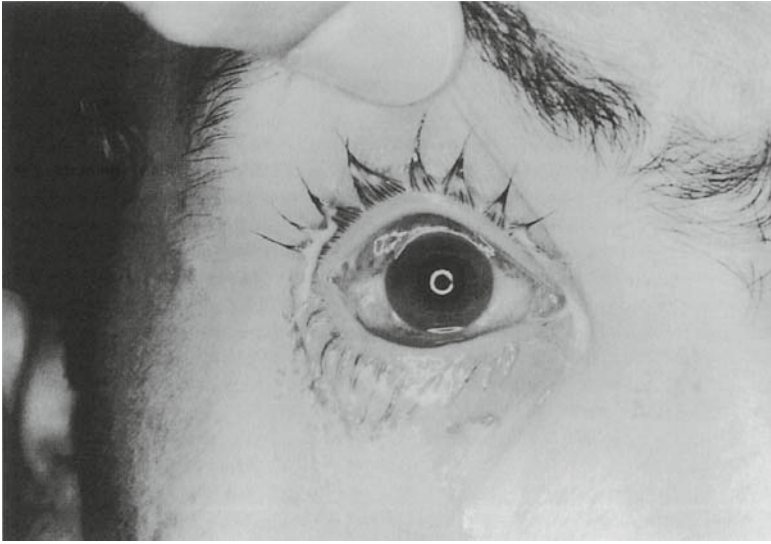
increasing the risk of ocular infections. Foreign bodies are another source of infections; for example, individuals who enjoy gardening or other outdoor activities are at increased risk for fungal infections of the cornea (keratitis) if the surface is abraded by organic matter such as a tree branch. Infections of the ocular surface include conjunctivitis and keratitis; less commonly, these infections can progress to include deeper layers (scleritis). Infections of the eyelid can progress to ulcerative blepharitis and evolve into preseptal or orbital cellulitis. Infections of the nasolacrimal system include canaliculitis and dacryocystitis. The Further Reading section of this chapter contains an article by Flowers that discusses in detail the evaluation and management of ocular surface and adnexal infections in older individuals and describes anatomic factors related to these infections.

### ***Epidemiology and Clinical Relevance***

There is an increased spectrum of bacteria that can be recovered from the eyelids of older individuals (2). With increasing age, there is a trend toward the recovery of more gram-negative bacteria, but *Staphylococcus epidermidis*, *Staphylococcus aureus*, and diphtheroids remain the predominant bacteria. The most common cause of infectious conjunctivitis is adenovirus; it is highly contagious and can result in epidemics among elderly patients in nursing homes (3). Infectious keratitis is recognized as a problem among elderly patients worldwide (4–7). Green and associates (6) identified a bimodal age distribution of patients with infectious keratitis, with one peak between the ages of 31–40 years and the other at >81 years. Risk factors for infectious keratitis differ between younger and older patients; infections in younger patients are frequently associated with contact lens wear while infections in older patients are more often associated with ocular surface disorders or systemic diseases (e.g., rheumatoid arthritis, diabetes mellitus) that can compromise the health of the cornea (4, 5). Elderly patients often have histories of blepharitis and corticosteroid use (7). The spectrum of causal organisms is the same as seen in the general population: coagulase-negative staphylococci, *S. aureus*, *Pseudomonas aeruginosa*, and fungi (4–6). Infectious keratitis in elderly patients tends to be more severe, with more complications and a worse prognosis, in part because of the association with ocular surface disease (5, 7). Laboratory studies in mice suggest that age-related alterations in immune function account for the increased severity of corneal infiltration with *S. aureus* (8) and *P. aeruginosa* (9) in elderly patients. Any damage to the cornea caused by infection leads to opaque scarring with profound vision loss.

### ***Clinical Manifestations***

Infections of the conjunctiva are characterized by redness and edema (chemosis) with variable erythema and swelling of the eyelids. Viral infections tend to cause watery discharge while bacterial and fungal infections result in purulence (Fig. 1).

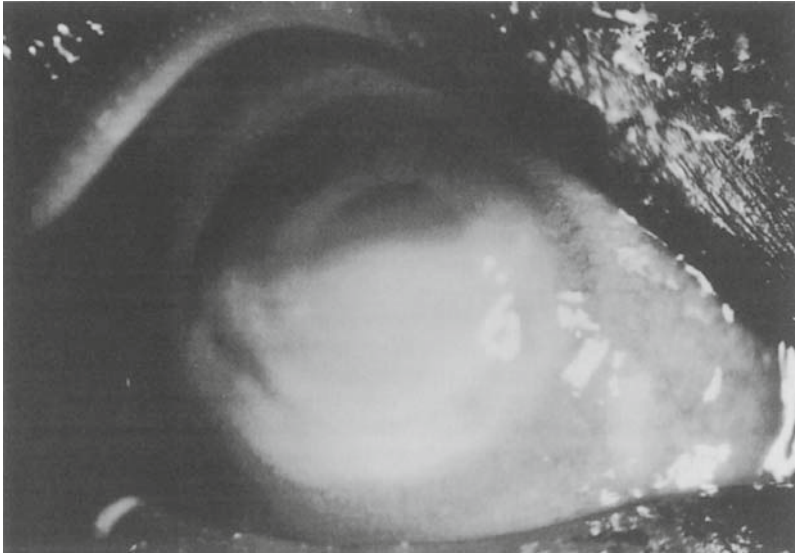


**Fig. 1** Bacterial conjunctivitis, characterized by eyelid swelling, conjunctival erythema, chemosis (edema of the conjunctiva), and purulent discharge. (Reprinted with permission from Flowers (1988). Managing eye infections in older adults. *Infectious Disease Clinical Practice*, 7:447–458.)

Most bacterial infections of the conjunctiva will be self-limited; persistent infections, especially if they persist despite treatment, suggest either reinoculation (e.g., from contamination of eye drops) or a nidus of infectious material (e.g., associated with a foreign body under the eyelid). Obstruction of the nasolacrimal drainage system can also serve as a reservoir of infectious material; the continuous reflux of organisms onto the ocular surface can overwhelm even intact natural defenses. A dacryocystitis should be suspected if there is erythema and tenderness near the medial canthus or reflux of mucopurulent material from the lower punctum with pressure over the same area. Conjunctival infections can progress to involve the cornea, resulting in dense, white infiltration of the corneal stroma (Fig. 2). Persistent infection can lead to progressive ulceration and perforation of the cornea.

### ***Diagnostic Tests***

Variations in the clinical features of infectious keratitis can sometimes suggest the causal agent to experienced clinicians; however, a culture is the only way to confirm a diagnosis. Cultures are also important because they provide antimicrobial sensitivity data, and they help to identify secular trends regarding causes of infections in specific communities (10). Infectious keratitis for which cultures have been negative or that,



**Fig. 2** Bacterial keratitis, characterized by ulceration and infiltration of the corneal stroma. (Reprinted with permission from Flowers (1988). *Managing eye infections in older adults. Infectious Disease Clinical Practice*, 7:447–458.)

despite treatment, are progressive can be evaluated with biopsy; specimens should be both cultured and examined histopathologically.

### ***Treatment***

There are no commercially available antiviral agents that will treat adenoviral conjunctivitis. Furthermore, the common practice of administering topical antibacterial agents to patients with viral conjunctivitis “to prevent secondary infection” is not necessary. Bacterial or fungal keratitis requires intensive topical antimicrobial therapy. Many clinicians will initiate therapy for small, community-acquired corneal ulcers with a single, commercially available topical antibiotic (usually a fluoroquinolone), without obtaining cultures. In contrast, because of the risk of resistant organisms and the severe consequences of a progressive infection, some corneal disease specialists believe that all cases of infectious keratitis should be treated with multiple “fortified” topical antibiotics obtained from a compounding pharmacy. Another controversy in management of infectious keratitis involves the use of corticosteroids; some clinicians believe that use of corticosteroids with antibiotics will decrease corneal scarring while others believe that the risks associated with suppression of the host’s immune response outweigh any potential benefit to be gained from the use of corticosteroids. It is recommended that all patients with

infectious keratitis be under the care of an ophthalmologist who can diagnose and monitor them for disease progression and complications such as impending perforation. Elderly patients may require hospitalization, at least early in the course of infection, to insure compliance with treatment regimens.

### ***Prevention***

A number of measures will reduce the risk of ocular surface infections among the elderly. Eyelid abnormalities should be corrected and dry eyes treated, to maintain natural barriers to infection. Blepharitis should be controlled to reduce resident flora on the eyelid margins. Corticosteroid use should be limited in the management of various ocular surface diseases, especially by non-ophthalmologists; it has been shown that prior corticosteroid use significantly increases the risk of antibiotic failure in the treatment of infectious corneal ulcers (11). Hand washing and other universal precautions should be practiced by all caregivers who may touch a patient's eyes. Nursing home residents who may have adenovirus conjunctivitis, especially those with mental status changes, should be isolated from other residents during the period of virus shedding (up to 14 days).

### **Herpetic Eye Disease**

Reactivation of varicella-zoster virus (VZV) in the first division of the Trigeminal nerve results in herpes zoster ophthalmicus (HZO, Fig. 3); as with other manifestations of herpes zoster, HZO is primarily a disease of older individuals, attributable to its association with waning of immunity (12, 13). Herpes simplex virus (HSV) keratitis is another important herpetic eye disease among the elderly, but its relationship to aging is less clear.

### ***Epidemiology and Clinical Relevance***

Butler and associates (5) found that HSV accounted for more cases of keratitis among older patients than among younger patients. Laboratory studies of mice suggest that older age is associated with more severe HSV keratitis (14); this change could not be attributed to increased virus load among infected animals, and investigators hypothesized that age-related changes in immune response accounted for their observations. A study in Rochester, MN, however, did not find a substantial age effect on the prevalence (149 cases/100,000 population; 95% confidence interval (CI), 115–183) or incidence (20.7 cases/100,000 person-years; 95% CI, 18.3–23.1) of HSV-associated eye disease (15). Also, in the National Institutes of Health (NIH)-funded Herpetic Eye Disease Study (HEDS), recurrent HSV keratitis was not influenced by the age of the patient (16).

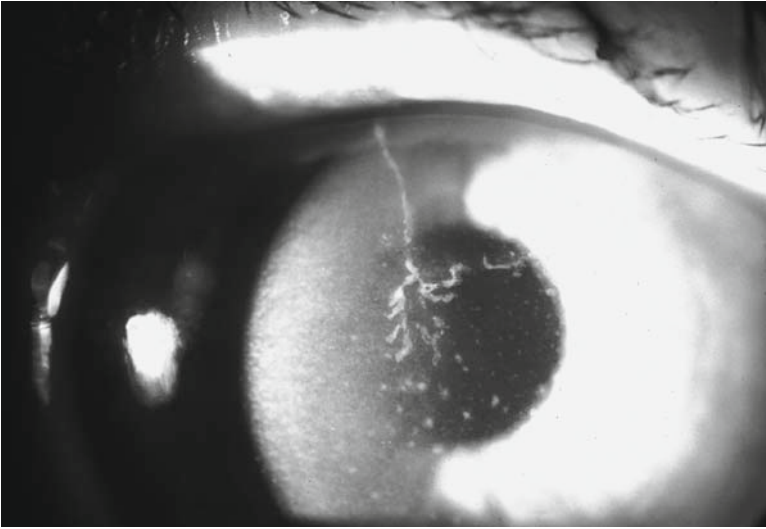


**Fig. 3** Herpes zoster ophthalmicus, resulting from involvement of the first division of the Trigeminal nerve. The presence of cutaneous lesions on the tip of the nose (Hutchinson sign) is associated with an increased risk of ocular involvement, as it indicates involvement of the nasociliary branch of the nerve, which also innervates the intraocular contents. (Reprinted with permission from Flowers (1988). *Managing eye infections in older adults. Infectious Disease Clinical Practice*, 7:447–458.)

As many as 30% of the general population will eventually develop some form of herpes zoster, and the risk of disease increases with age; as many as 50% of people  $\geq 85$  years of age will develop the disease (12) (see also the chapter “Herpes Zoster”). HZO accounts for 10–20% of herpes zoster cases and ocular involvement occurs in up to 50% of people with HZO (12).

### ***Clinical Manifestations***

There are many forms of herpetic eye disease; findings depend in the relative contributions of productive viral infection and the immune response to viral antigen (or possibly to altered host tissue). The classic lesion of HSV-related eye disease is the dendrite, corresponding to a productive HSV infection of the corneal epithelium. It can be associated with redness, tearing, and irritation, but an isolated



**Fig. 4** “Late pseudodendrites” in a patient with a history of herpes zoster ophthalmicus. These corneal epithelial lesions contain varicella-zoster virus DNA, and will resolve with topical or systemic antiviral therapy

dendrite itself may be difficult for non-ophthalmologists to visualize, as it is not associated with any corneal opacification. Dendrites are best seen with fluorescein staining. Inflammatory disorders include stromal keratitis (characterized by dense infiltration and vascularization of the cornea) and disciform keratitis (reversible dysfunction of the corneal endothelial with overlying stromal edema).

Ocular complications of HZO include conjunctivitis, episcleritis, and scleritis; various forms of corneal inflammation that are similar to HSV-related diseases (stromal keratitis, disciform keratitis); anterior uveitis, optic neuritis, and cranial nerve palsies. Ocular involvement is more likely to be severe and chronic in nature among older patients. An under-appreciated complication of HZO is development of “late pseudodendrites” (Fig. 4), which can occur months after resolution of skin vesicles (13). These corneal epithelial lesions are pleomorphic but tend to be more irregular and lacy than classic HSV dendrites. They contain VZV DNA and will respond to antiviral treatment. (Interested readers are directed to references in the Further Reading section of this chapter for in-depth discussions of the complex clinical spectrum of herpetic eye diseases.)

### ***Diagnostic Tests***

HSV can be identified in dendrites by culture or polymerase chain reaction (PCR) techniques, but the typical appearance of these lesions allows a clinical diagnosis in most cases; however, virus will not be recovered from most HSV-associated



inflammatory lesions. The diagnosis of VZV-associated eye disease is rarely a problem because of its association with the antecedent dermatomal skin vesicles. As noted above, VZV DNA can be identified in late pseudodendrites.

### ***Treatment***

The management of HSV-associated eye disease is complex, requiring antiviral agents or corticosteroids or both, depending on the nature of the specific presentation. Dendrites can be treated with topical or oral antiviral medications, but the concurrent use of both is not necessary. Indiscriminant use of corticosteroid can exacerbate productive HSV infections. (The management of HSV keratitis, based on various HEDS trials, is summarized in an article by Sudesh and Laibson that is included in the Further Reading section.)

During the period of active cutaneous vesicles, oral antiviral treatment of HZO will reduce the incidence and severity of ocular involvement, but continuation of antiviral therapy for patients with ocular involvement will have little effect after resolution of the skin lesions. Resumption of antiviral therapy is appropriate for patients who develop late pseudodendrites.

### ***Prevention***

Oral acyclovir (400 mg orally twice daily) has been shown to reduce the incidence of recurrent HSV keratitis (17). In the original study (17), patients were treated for 1 year, but some clinicians will administer prophylactic acyclovir indefinitely to patients at high risk of recurrence. The zoster vaccine is recommended by the Centers for Disease Control and Prevention for all adults over 60 years of age; however, because the vaccine boosts cell-mediated immunity against VZV, it is possible that people with histories of HZO and keratitis or uveitis will have an exacerbation of the inflammatory component of their eye disease if vaccinated.

### ***Exogenous Endophthalmitis***

Infection of the intraocular spaces (endophthalmitis) is an uncommon but a potentially devastating complication of cataract surgery. It is an infection of older patients by virtue of the fact that most cataracts are age-related, but even among all patients undergoing surgery, older patients are at increased risk of infection, as described below. Postoperative infections can also occur in patients with glaucoma who have undergone trabeculectomy, a procedure that creates a channel from inside the eye to the subconjunctival space; the resulting “bleb” can become infected with bacteria

from the eyelid margins with the eventual spread of organisms inside the eye. Other causes of exogenous endophthalmitis in older patients include penetrating trauma associated with falls and contiguous spread of infection from other sites (e.g., the orbit or perforated corneal ulcers).

### ***Epidemiology and Clinical Relevance***

In a review of Medicare claims data, West and associates (18) determined an incidence for post-cataract surgery endophthalmitis of 2.15/1,000 surgeries over the period 1994–2001. They found that older age was independently associated with an increased risk of endophthalmitis (relative risk (RR), 1.83; 95% CI, 1.19–2.81 for patients  $\geq 90$  years of age). In their article, the authors cited other studies that came to the same conclusion. Older age may be a risk factor for a variety of reasons: longer surgical time because of greater lens density, impaired wound healing, reduced host defenses, or poor compliance to postoperative care regimens. Diabetics also have a worse prognosis.

Infections that become apparent within a few days of surgery are most commonly caused by coagulase-negative staphylococci or other gram-positive organisms from the eyelid margins. A chronic form of low-grade endophthalmitis can be caused by organisms of lower virulence such as *Propionibacterium acnes*; in such cases, symptoms and signs of infection may not be apparent for weeks or months after surgery. With aggressive treatment, infection can be eliminated and useful vision retained in many cases, but postoperative endophthalmitis can lead to loss of the eye, when infection is associated with more virulent organisms such as gram-negative bacteria.

### ***Clinical Manifestations***

Signs of endophthalmitis include redness and chemosis, swelling of the eyelids, clouding of the cornea, and hypopyon (layering of leukocytes in the inferior angle of the anterior chamber) that are out of proportion to usual post-operative findings. Infection is suggested by the symptoms of pain and decreased vision. Early signs of bleb-associated infections include localized redness and exudation at the site of the bleb. Symptoms and signs are eventually similar to those described for endophthalmitis after cataract surgery.

### ***Diagnostic Tests***

Identification of the infecting organism requires aspiration of vitreous humor for microscopic examination and culture.

## ***Treatment***

Immediate treatment is required for successful retention or recovery of vision. All patients with exogenous endophthalmitis should be treated with intravitreal injections of broad-spectrum antibiotics until culture results are known. Other factors in the management of post-cataract surgery endophthalmitis were clarified by the National Institutes of Health-funded Endophthalmitis Vitrectomy Study (EVS) (19). For patients who develop endophthalmitis within 6 weeks of surgery, systemic antibiotics offer no additional benefit. Vitrectomy improves visual outcomes for those patients who present with reduced vision to the “light perception only” level; in contrast, complete removal of the vitreous humor before intravitreal injection of antibiotics did not improve outcomes for patients who present with visual acuity better than light perception. The majority of patients treated in the EVS (53%) achieved visual acuities of 20/40 or better (19).

## ***Prevention***

Patients and caretakers can help to reduce the risk of postoperative infections by controlling blepharitis with eyelid hygiene before surgery to reduce flora on the eyelid margins and, if prescribed by the surgeon, by the use of preoperative topical antibiotics.

## **Endogenous Infections of the Retina and Choroid**

Bacteria, fungi, viruses, and parasites can reach the eye via the bloodstream to cause infections of the choroid, the retina, or both. Fungal or bacterial infections can be metastatic, from a non-ocular site of infection or they can result from introduction of organisms into the bloodstream during medical procedures. These infections can progress to involve the aqueous or vitreous humor (endogenous endophthalmitis). Candidal chorioretinitis is the most common of the fungal infections. ARN syndrome, caused by either HSV or VZV, is the most common viral retinopathy. Ocular toxoplasmosis is the most common retinal infection overall and will be presented in the next section.

Despite the diversity of these disorders, endogenous infections share a number of features in common. Despite hematogenous seeding of organisms, infections are often unilateral. There may be no obvious precipitating event, and redness can initially be misinterpreted as “pink eye,” a term usually used by non-ophthalmologists to imply mild, self-limited viral conjunctivitis. Pain and markedly decreased vision provide important clues to the presence of intraocular disease; however, pain is sometimes absent. Prognosis depends on the virulence of the organism,

the location of the infection inside the eye, and the duration of infection before treatment. A high suspicion for infection, with early referral to an ophthalmologist is critical. It is also important to distinguish ocular infections from masquerade syndromes such as large cell lymphoma, which can resemble endophthalmitis.

### *Epidemiology and Clinical Relevance*

Fungal and bacterial infections are associated with debilitating systemic diseases (diabetes mellitus, malignancy, liver disease, alcoholism), and thus, patients tend to be older. In a classic description of candidal chorioretinitis by Edwards and associates (20), 34 patients with proven or presumed/possible infection at UCLA Medical Center and its affiliate Harbor-UCLA Medical Center ranged in age from 17 to 79 years (median 54 years), but over a third were 60 years of age or older; however, in a study of 38 patients, Park and associates (21) did not find that age was a specific risk factor for ocular infection among patients with candidemia. Candidal infections are associated with a variety of specific, and often interrelated, risk factors (20); they include major surgery (especially involving the gastrointestinal tract), bacterial sepsis, systemic antibiotic use, and indwelling intravenous catheters (especially with hyperalimentation) (see also the chapter “Fungal Infections”). *Candida* spp., are frequently present in the normal gastrointestinal tract, and surgical manipulation of the bowel can cause seeding of the blood stream. Patients undergoing abdominal surgery may also be on antibiotics, which allow overgrowth of fungi in the gut, and they may also require hyperalimentation.

Endogenous bacterial endophthalmitis can arise from a variety of non-ocular infections, including liver abscesses, septic arthritides, skin wounds, and urinary tract infections, especially among debilitated patients. In a review of the medical literature, Jackson and associates (22) found that *Klebsiella pneumoniae* was the most common cause of endogenous bacterial endophthalmitis and was associated specifically with liver abscesses. They also described a 3% risk of intraocular infection among patients with *K. pneumoniae* liver abscesses. Other commonly reported bacteria include *S. aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitides*, and other gram-negative organisms. Bacterial endophthalmitis may be the first confirmation of septicemia, although patients often have non-specific preceding symptoms such as fever or arthralgias.

There is a statistical difference in the ages of patients with ARN syndrome caused by different viruses; those with VZV-associated ARN syndrome are older than those with disease caused by HSV-1 or HSV-2 (23). Disease is thought to be associated with reactivation of latent virus; the age difference may reflect different timing of initial infection, as HSV-2-associated ARN is thought to be a late complication of congenital infection (23). ARN syndrome in older patients may or may not be preceded by cutaneous herpes zoster.

## ***Clinical Manifestations***

Early symptoms and signs of any endogenous infection may be similar to those associated with exogenous endophthalmitis: redness and chemosis, eyelid swelling, pain, and reduced vision. With regard to the fundus, candidal infections are usually multifocal, with small chorioretinal lesions progressing rapidly into the vitreous humor rather than spreading within the choroid or retina. Signs of bacterial infections are highly variable because septic emboli can lodge in any intraocular tissue (iris, ciliary body, choroid, retina), but corneal haze, a sluggish pupil, and hypopyon are common, regardless of the site of infection. ARN syndrome is characterized by large, wedge-shaped areas of retinal whitening, severe inflammatory reactions, and retinal vascular occlusions are common.

## ***Diagnostic Tests***

Although there can be some clinical findings in the fundus that will help to distinguish between different infections, it can be difficult for even ophthalmologists to see the back of the eye clearly because of intense inflammation; diagnosis may therefore depend on systemic disease associations and laboratory evaluation of intraocular fluids using culture or PCR techniques. Blood cultures have been positive in the majority of reported cases of endogenous bacterial endophthalmitis. Catheter tips should be cultured in suspected cases of fungal endophthalmitis.

## ***Treatment***

In contrast to exogenous endophthalmitis, systemic antimicrobial therapy plays an important role in the management of endogenous infections. In the early stages of infection, when organisms are confined to the choroid or retina, systemic antimicrobial therapy alone may cure the intraocular infection. Because intraocular disease can be the first manifestation of disseminated infections, treatment can also be life-saving. Once organisms have extended into the vitreous cavity, because of the low drug concentrations achieved in the vitreous humor, systemic therapy alone is less likely to cure infection. Supplemental intravitreal injections of antibacterial or antifungal agents are therefore used.

Amphotericin B is the gold standard for treatment of candidal chorioretinitis, but treatment is difficult because of drug toxicity. Many clinicians now favor treatment with oral fluconazole or voriconazole; however, treatment with these agents must be monitored closely because certain *Candida* spp., are resistant to fluconazole and others can develop resistance to the drug.

ARN syndrome is treated initially with high-dose intravenous acyclovir. Many clinicians will also administer intravitreal injections of ganciclovir or foscarnet

not because of infection in the vitreous humor but to increase retinal tissue levels of drug; however, the need for such injections has not been confirmed.

### ***Prevention***

Treatment of non-ocular infections will limit the risk of dissemination. Screening eye examinations should be performed on at-risk patients to identify intraocular infections early when they are more amenable to treatment. A several-month course of oral acyclovir (or comparable antiviral agent) after resolution of unilateral ARN syndrome is believed to reduce the incidence of second eye involvement.

### **Ocular Toxoplasmosis**

Toxoplasmic retinochoroiditis is the most common infection of the retina in the general population (24, 25). Acquisition of the causal agent, *Toxoplasma gondii*, occurs through ingestion of water or uncooked fruits or vegetables contaminated with cat feces that contains parasite oocysts (the cat is the only definitive host; sexual reproduction of the parasite occurs in the gut) or through ingestion of dormant parasite tissue cysts in undercooked meat of various food animals (intermediate hosts that become infected, but in which sexual reproduction of the parasite does not occur). The infection usually results in no systemic symptoms. Parasites that reach the eye through the bloodstream can cause a focal infection of the retina, characterized by localized retinal necrosis and intense inflammation. In immunocompetent individuals, these parasites do not spread to infect other ocular tissues, and they eventually become latent (but viable) tissue cysts with spontaneous resolution of the active retinal lesion. These tissue cysts can reactivate, even years later, to cause additional episodes of toxoplasmic retinochoroiditis. In some cases, the initial retinal infection is subclinical; only with reactivation of the tissue cysts does clinical disease occur.

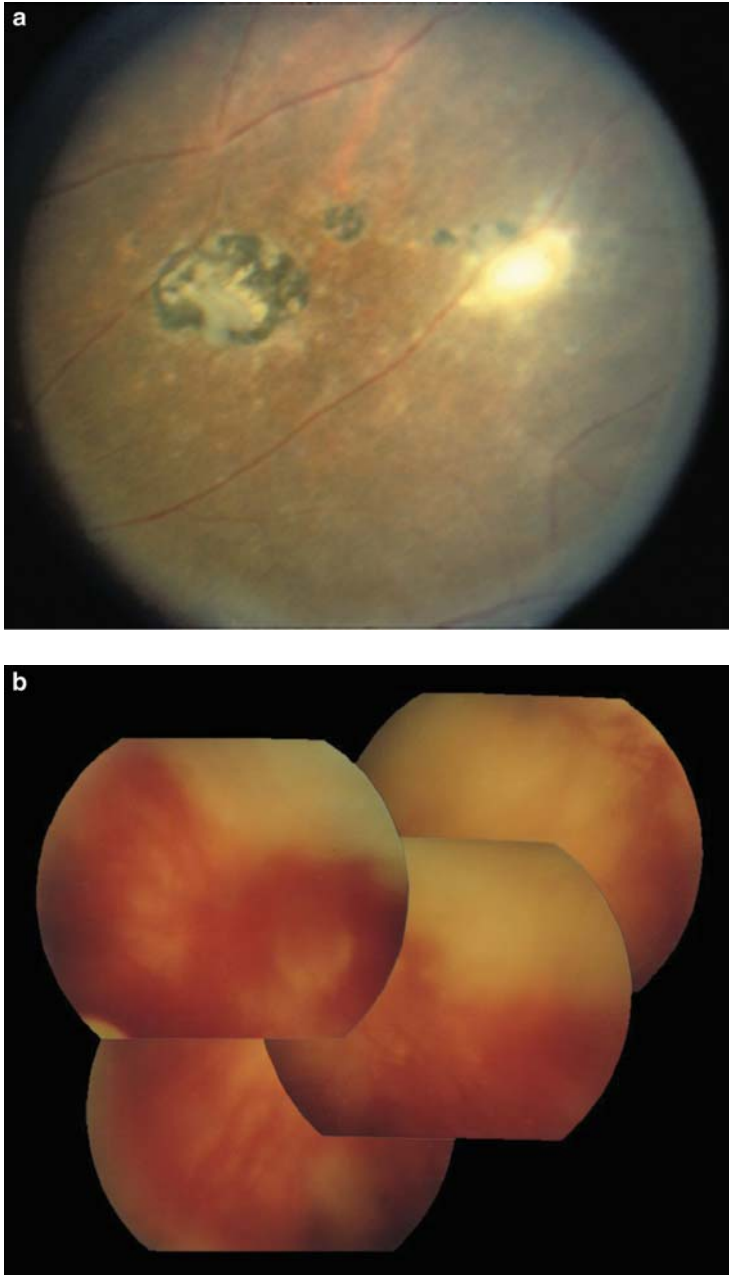
### ***Epidemiology and Clinical Relevance***

In the United States, 22.5% of the population have antibodies against *T. gondii*, but it has been estimated that only 2% of those individuals have ocular lesions (24, 25). Seroprevalence increases with age. In some other areas of the world, infection is even more common, and ocular involvement is more prevalent among infected people. Depending on the size of lesions and their location in the fundus, toxoplasmic retinochoroiditis can result in vision loss.

It is generally believed that in older individuals ocular toxoplasmosis is a more severe disease. Holland (24, 25) has summarized the evidence that age is a risk factor, as follows. Researchers in the Netherlands have found that patients with ocular toxoplasmosis who have serologic evidence of recent infection are older on average than those with serologic evidence of remote infection. In a 1995 epidemic of *T. gondii* infection in Victoria, British Columbia, Canada, the mean age of infected patients without retinal lesions was approximately 28 years whereas the mean age of infected individuals with eye disease was 54 years. In southern Brazil, the proportion of individuals older than 40 years of age who develop ocular toxoplasmosis during the first 2 years after *T. gondii* infection is greater than the proportion among those who are younger. In the United States, a higher proportion of patients older than 40 years of age have prolonged episodes and loss of vision than younger patients. Although much of this evidence is circumstantial, the consistency of these various observations suggests (1) that older patients have a higher risk of developing ocular lesions following recently acquired *T. gondii* infection, and (2) that episodes of toxoplasmic retinochoroiditis are more prolonged and have a worse prognosis in older patients. Since the review by Holland, another study from Brazil showed that age was the major risk factor for the presence of ocular disease among household members infected with *T. gondii* (26); the prevalence of ocular toxoplasmosis was significantly higher among those older than 50 years.

### ***Clinical Manifestations***

Initial (primary) lesions are characterized by discrete foci of dense, white retinal inflammation. Once established, lesions do not appear to enlarge appreciably, and they eventually heal (usually over a 4- to 6-week period), leaving a retinochoroidal scar with variable amounts of pigmentation. Recurrent lesions tend to arise from the borders of such scars (Fig. 5a). Patients can have multiple scars, but there is rarely more than one focus of active disease with any given recurrence. Active lesions can be associated with secondary vitreous humor and anterior segment inflammatory reactions of varying severity. Patients may complain of redness, pain, and photophobia. Lesion characteristics can be more severe in elderly patients (Fig. 5b). Among 34 patients in two publications that focused specifically on older patients (27, 28) (mean age 67.1 years; median age 67.5 years; range 50–87 years), at least 22 patients had one or more of the following features: multiple active lesions; large lesions (>3 optic disc areas in size); or prolonged disease (>8 weeks in duration). In addition, 20 patients (59%) did not have pre-existing retinochoroidal scars, and at least 14 patients (41%) had anti-*T. gondii* IgM antibodies, suggesting that infection was recently acquired. Thus, in this older population, the severity of disease could not be attributed to the cumulative effect of many years of recurrences. Recurrences can be seen many years after the first episode of toxoplasmic retinochoroiditis, but the risk of recurrence falls as the interval after an active episode increases (29).



**Fig. 5** (a) Classic appearance of recurrent toxoplasmic retinochoroiditis arising from a retinochoroidal scar. (b) Extensive retinal necrosis caused by persistent *Toxoplasma gondii* infection in an elderly patient. (Reprinted from Holland (2004). Ocular toxoplasmosis: a global reassessment. Part II: Disease manifestations and management. *American Journal of Ophthalmology*, 137:1–17, with permission from Elsevier, Inc.)



The risk at any point is higher in older patients (RR, 1.74; 95% CI, 1.06–2.86;  $p = 0.03$  for patients  $\geq 40$  years of age).

### ***Diagnostic Tests***

Diagnosis is based primarily on the appearance of lesions. A negative serologic test for *T. gondii* antibodies helps to exclude a diagnosis of ocular toxoplasmosis in a patient with retinal lesions, but a positive test does not confirm a diagnosis, as 40% or more of individuals in the United States are seropositive after the seventh decade (24, 25). A more definitive test is identification of parasitic antigen by PCR techniques on ocular fluid. Because of the potential morbidity of removing aqueous or vitreous humor from the eye, such testing is not routine; a therapeutic challenge may be more appropriate in cases for which suspicion of toxoplasmosis is high.

### ***Treatment***

Toxoplasmic retinochoroiditis is usually treated with a finite course of one or more antimicrobial drugs to hasten the resolution disease activity. Treatment is usually administered only during the period of active disease, as no currently available agent is active against tissue cysts. The most commonly used regimen includes pyrimethamine and sulfadiazine, but many other agents have been used. Most patients are also treated concurrently with oral corticosteroids to reduce the risk of tissue damage by the associated inflammatory response. Large lesions of long duration in elderly patients may reflect prolonged replication of parasites, possibly because of impaired immune function; it may be prudent to withhold concurrent corticosteroids in such cases, to avoid further suppression of host defenses. (The Further Reading section contains an article by Holland and Lewis that reviews in detail various drug regimens used to treat toxoplasmic retinochoroiditis.)

### ***Prevention***

There are two issues to consider in terms of prevention: prevention of *T. gondii* infection among those who remain seronegative, and prevention of recurrent disease among people with prior episodes of toxoplasmic retinochoroiditis. Thorough cooking of meat (to destroy tissue cysts) and washing of uncooked fruits and vegetables (to destroy oocysts) will prevent transmission of the parasite to people not yet infected. Unfiltered water from non-commercial sources should be avoided. To prevent recurrent toxoplasmic retinochoroiditis, some clinicians will administer secondary prophylaxis to high-risk patients, especially those with vision-threatening lesions, based on studies in southern Brazil (30). The most common regimen is

a commercially available combination of trimethoprim (160 mg)-sulfamethoxazole (800 mg), given once every 3 days, for at least 2 years, the period of highest risk for recurrences (29).

## Summary

The medical literature is replete with articles that identify aging as a risk factor for ocular infections. This chapter has provided only a sampling of such references, but they serve to illustrate several general principles regarding evaluation and management of ocular infections in older patients, as listed below:

- The risk of many ocular infections can be reduced. It is especially important to maintain natural defenses by repairing anatomic abnormalities of the eyelids, maintaining a moist ocular surface, and correcting obstruction of the nasolacrimal system. Trauma and exposure to pathogens should be avoided. For example, patients should wear protective eye gear with activities such as gardening; blepharitis should be treated; and contamination of medications should be prevented.
- Maintenance of good general health will reduce the risk of infection and facilitate the resolution of infections, if they occur. In particular, systemic problems that can lead to septicemia or fungemia should be treated promptly.
- Early recognition of infection is critical. Redness and chemosis, sudden changes in vision, and ocular pain should be evaluated promptly. Because ocular tissues are delicate and do not regenerate with normal function when damaged, prompt attention to infections is critical to retain sight.
- Accurate diagnosis of ocular infections can be difficult. Primary care providers must not assume that all red eyes are conjunctivitis; several disorders can superficially resemble one another at onset, despite marked differences in pathogenesis, diseases severity, and prognosis. Intraocular infections, for example, can result in redness, chemosis, and eyelid swelling that is mistaken initially for an ocular surface infection. Pain and change in vision provide clues to the more serious nature of intraocular disease. Misdiagnosis and delay in treatment can have devastating consequences; therefore, early referral to an ophthalmologist is critical. Accurate diagnosis may require knowledge of multiple factors: course of disease, clinical findings obtained with specialized ophthalmic equipment, and, in some cases, invasive diagnostic tests or even therapeutic trials.
- Treatment of ophthalmic infections should be aggressive. Treatment may require supervision to ensure that it is administered correctly. Use of corticosteroids should be limited, if used at all.

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# Otitis Externa, Otitis Media, and Sinusitis

Vinod K. Dhawan

## Key Points

- *Pseudomonas aeruginosa* malignant otitis externa, which can be a life-threatening infection if not diagnosed and treated promptly and appropriately, is typically seen in elderly diabetics.
- Local debridement, topical combination agents (antipseudomonal antibiotic with corticosteroids), and systemic antipseudomonal antibiotics is the treatment of choice for *P. aeruginosa* malignant otitis externa.
- Acute otitis media occurs less commonly in older adults than in children, and it is most commonly caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*; high-dose amoxicillin is the current drug of choice.
- Acute sinusitis is generally preceded by a viral infection; the presence of purulent nasal discharge or pharyngeal discharge and cough persisting for over a week following a “cold” should prompt a consideration of acute sinusitis.
- Sinusitis may be complicated by serious intracranial suppurative processes such as meningitis, brain abscess, subdural empyema, or epidural abscess.

## Otitis Externa

Otitis externa is an inflammatory condition involving the superficial layer of the external auditory canal. Otitis externa can take an acute or a chronic form, with the acute form affecting four in 1,000 persons annually and the chronic form affecting 3–5% of the population (1). Acute otitis externa in the elderly is generally a benign disorder, which may be localized or generalized. Acute localized otitis externa is

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furunculosis of the outer third of the ear canal and is usually a staphylococcal infection. Acute diffuse otitis externa (swimmer's ear) is generally due to *Pseudomonas aeruginosa*. It is triggered by irritation and maceration of the skin of the ear canal and related to excessive moisture and loss of protective cerumen. Chronic otitis externa is caused by irritation due to the drainage from the middle ear in patients with chronic suppurative otitis media. An uncommon form of external otitis called "malignant otitis externa" is a rare but a potentially serious disease of the external auditory canal seen mostly among elderly, diabetic, or immunocompromised patients. It is an invasive and necrotizing infection that spreads from the squamous epithelium of the ear canal to the surrounding soft tissues, cartilage, bones, and even cranial nerves (2). It can be fatal if treatment is not aggressive and timely.

### ***Epidemiology and Clinical Relevance***

Otitis externa is observed more frequently during the summer months, as the maceration of the skin lining the external auditory meatus is facilitated by heat, humidity, and perspiration. Swimming may lead to otitis externa by introducing moisture into the ear canal. Malignant otitis externa is typically seen in elderly diabetics in whom chronic hyperglycemia, tissue hypoperfusion due to microangiopathy, altered cell-mediated immunity, and impaired phagocytic function all play a pathogenic role. Occasionally, malignant otitis externa has been noted after syringing of the ear canal (3). Acute disease commonly results from bacterial (90% of cases) or fungal (10% of cases) overgrowth in an ear canal subjected to excess moisture or to local trauma. Acute otitis externa is generally caused by organisms such as *Staphylococcus aureus* and *P. aeruginosa*. Malignant otitis externa is almost always due to *P. aeruginosa*. Only rare cases of malignant otitis externa are due to *S. aureus* (4), *Proteus mirabilis* (5), and *Aspergillus fumigatus* (6) have been reported. Chronic disease is a part of more generalized dermatologic or allergic problem. Rare causes of chronic otitis externa include tuberculosis, fungal infections, syphilis, yaws, leprosy, and sarcoidosis. Fungal otitis externa may be part of a general or local fungal infection; *Aspergillus* spp. are responsible for most cases (7).

### ***Clinical Manifestations***

Acute otitis externa causes ear pain that may be quite severe due to the limited space for expansion of the inflamed tissue. The movement of the external ear and sometimes of the jaw aggravates the pain. The patients may experience itching of the ear. The infection typically starts at the junction of the cartilage and bone in the external meatus. Speculum examination of the canal reveals the skin to be edematous and erythematous. There may be an accumulation of moist debris in the canal. The tympanic membrane may be difficult to visualize and may be mildly inflamed

but is normally movable on insufflation. Acute localized otitis externa may occur as a pustule or furuncle associated with the hair follicles. *S. aureus* is generally the causative organism in these patients. Infection due to Group A streptococcus may cause erysipelas of the concha and the canal. Examination may reveal hemorrhagic bullae in the ear canal or on the tympanic membrane and a regional lymphadenopathy may be noted.

In the elderly, most episodes of otitis externa resolve completely within 5–7 days. Failure of resolution of otitis externa should lead to suspicion of malignant otitis externa, especially in elderly diabetics. Such patients have an unremitting otalgia, a tenderness of the tissues around the ear and mastoid, and a purulent drainage from the canal. Examination of the ear canal reveals granulation tissue at the osseous–cartilaginous junction. The progression of malignant otitis externa along Santorini’s fissure and into the mastoid may lead to facial nerve palsy. The infection may further spread to jugular foramen at the base of skull and involve the glossopharyngeal, vagus, and spinal accessory nerves. Similarly, extension of infection into the hypoglossal canal may involve the hypoglossal nerve and involvement of the petrous apex may lead to the abducent and trigeminal nerves palsies. Other potential complications of malignant otitis externa include jugular venous thrombosis, cavernous sinus thrombosis, and meningitis (see Table 1).

### Diagnostic Tests

The white blood cell count may be elevated in acute otitis externa, but this finding is nonspecific. The erythrocyte sedimentation rate is usually very high in patients with malignant otitis externa and may be useful in monitoring therapy (8). Cultures from the granulation tissue or the involved bone will reveal the organism. Definitive diagnosis of malignant otitis externa is frequently elusive, requiring a high index of suspicion, various laboratory and imaging modalities, and histologic exclusion of malignancy. Plain film radiography is inadequate for its evaluation. Technetium<sup>99</sup>

**Table 1** Salient features of malignant otitis externa in the elderly

Predisposing factors	<ul style="list-style-type: none"> <li>• Diabetes mellitus</li> <li>• Immunocompromise</li> </ul>
Microbiology	Usually due to <i>Pseudomonas aeruginosa</i>
Complications	<ul style="list-style-type: none"> <li>• Cranial nerve palsies (facial, glossopharyngeal, vagus, spinal accessory, hypoglossal, abducent and trigeminal)</li> <li>• Jugular venous thrombosis</li> <li>• Cavernous sinus thrombosis</li> <li>• Meningitis</li> </ul>
Therapy	<ul style="list-style-type: none"> <li>• Aminoglycoside + antipseudomonal penicillin (piperacillin, ticarcillin, etc.) or</li> <li>• Aminoglycoside + ceftazidime or</li> <li>• Quinolones: ciprofloxacin, ofloxacin</li> </ul>

bone scans and gallium<sup>67</sup> scans are very sensitive but not very specific (9, 10). Bone scans may remain positive long after the microbiologic cure of this condition and, therefore, are not very useful in monitoring the response to therapy. The extent of damage to the soft tissue and bone may be identified and monitored by use of computed tomography (CT) and magnetic resonance imaging (MRI). Single photon emission computed tomography (SPECT) bone imaging may complement CT or MRI for initial diagnosis of malignant otitis externa. Routine SPECT bone imaging further supplemented by gallium scintigraphy may be useful in the follow up of these cases for assessing response to treatment and disease recurrence (11).

## **Therapy**

The American Academy of Otolaryngology-Head and Neck Surgery Foundation has recently provided guidelines for the management of otitis externa (12). The recommendations include an assessment of pain and analgesic treatment based on its severity. Acute otitis externa should be distinguished from other causes of otalgia, otorrhea and inflammation of the ear canal. The management of uncomplicated otitis externa consists of gentle cleansing of the external auditory canal to remove debris and instillation of appropriate topical antibiotics (12, 13). Topical antimicrobial therapy is highly effective for acute otitis externa with clinical cure rates of 65–80% within 10 days of therapy (14). Systemic antibiotic therapy is reserved for advanced disease or for immunocompromised individuals. The ear canal may be irrigated with hypertonic saline (3%) or cleansed with mixtures of alcohol (70–95%) and acetic acid. Inflammation of the canal may be reduced with hydrophilic solutions such as 50% Burrow solution. Ear drops of topical antibiotics combined with a corticosteroid preparation (e.g., topical ciprofloxacin 0.3%/dexamethasone 0.1% otic suspension or polymyxin B/neomycin/hydrocortisone otic suspension) diminish the local inflammation (15). Ciprofloxacin ear drops may provide faster pain relief than polymyxin B/neomycin (16). The placement of a wick in the ear canal may facilitate the delivery of antibiotic drops into the ear canal. Incision and drainage of the furuncle may be necessary to relieve severe pain.

If the patient fails to respond to the initial therapeutic option within 48–72 h, then the clinician should reassess the patient to exclude other causes of illness. Malignant otitis externa is treated with local debridement of the canal and topical treatment with antipseudomonal antibiotics combined with corticosteroids. Additionally, systemic therapy directed at *P. aeruginosa* should be used for 4–6 weeks. The combination of a ceftazidime or an antipseudomonal penicillin (e.g., piperacillin) with an aminoglycoside (gentamicin or tobramycin) should be considered for synergy. Oral quinolones with activity against *P. aeruginosa* such as ciprofloxacin and levofloxacin are generally effective. Some consider ciprofloxacin to be the drug of choice due to its high concentration in the bone and cartilage, the ease of oral administration, and its low toxicity (17). Bacterial isolates must be tested for sensitivity to antibiotics, since resistance to quinolones is emerging



among strains of *P. aeruginosa* (18). No clear evidence exists to demonstrate the efficacy of hyperbaric oxygen therapy as compared to treatment with antibiotics and/or surgery (19).

### ***Prevention***

Preventive measures reduce recurrences and typically involve minimizing ear canal moisture, trauma, or exposure to materials that incite local irritation or contact dermatitis. Use of a blow dryer after swimming to dry the ear canal has been suggested as a preventive measure. Aggressive cleansing of the ear canal should be avoided since the resulting disruption of its lining and subsequent invasion by resident bacterial flora may lead to infection. Prompt recognition of malignant otitis externa and its aggressive therapy will minimize its devastating complications.

### **Otitis Media**

While infrequent among the elderly, infection of the middle ear may be the cause of fever, significant pain, and impaired hearing. Acute otitis media or inflammation of the middle ear is defined by the presence of fluid in the middle ear and accompanied by the symptoms or signs of illness. The simple presence of fluid in the middle ear without clinical symptoms or signs of active infection is referred to as otitis media with effusion. Acute otitis media is considered to be recurrent when three new episodes of acute otitis media have occurred in 6 months or four episodes within 12 months. The term chronic otitis media refers to a prolonged duration of middle ear effusion usually resulting from a previous episode of acute infection. The epithelial lining of the middle ear contains ciliated cells, mucus-secreting goblet cells, and cells capable of secreting local immunoglobulins. The middle ear secretions drain into the nasopharynx through the Eustachian tube. The pathogenesis of otitis media involves interactions among host characteristics, virulence factors of viral and bacterial pathogens, and the environmental factors. Conditions resulting in obstruction of the Eustachian tube, including congestion of the mucosa during viral infections, play a critical role in the development of otitis media. Bacterial pathogens may infect the middle ear secretions accumulated behind the obstruction leading to otitis media.

### ***Epidemiology and Clinical Relevance***

Acute otitis media has been best studied in children in whom the disease is particularly common (20). Few studies have addressed the epidemiology of middle ear infec-

**Table 2** Bacterial pathogens in acute otitis media

Pathogen	Mean %	Range %
<i>Streptococcus pneumoniae</i>	39	27–50
<i>Haemophilus influenzae</i>	30	17–50
<i>Moraxella catarrhalis</i>	10	6–27
<i>Streptococcus pyogenes</i>	3	2–6

tions in the elderly. In 1990, there were an estimated 24.5 million visits made to offices of physicians in the United States at which the principal diagnosis was otitis media (21). Acute otitis media occurs more often in males than in females and likely has a genetic susceptibility. Native Americans, Alaskan and Canadian Eskimos, and Australian Aborigines have an extraordinary incidence and severity of otitis media. The single most frequently recognized cause of acute otitis media is a viral upper respiratory tract infection. Others have anatomic changes (cleft palate, cleft uvula, submucous cleft), alteration of normal physiologic defenses (patulous Eustachian tube), congenital or acquired immunologic deficiencies, including acquired immunodeficiency syndrome. A relationship has been suggested between gastroesophageal reflux and otitis media with effusion in adults (22).

Bacteria are found in 50–90% of cases of acute otitis media with or without otorrhea, and viruses are found in 20–49% of cases (23). In many cases, both bacteria and viruses are found (23). The bacterial agents recovered most frequently from patients with acute otitis media are *Streptococcus pneumoniae*, nontypable *Haemophilus influenzae*, *Moraxella catarrhalis*, and Group A streptococcus (Table 2). In approximately 10% of patients, the otitis media may be caused by type b *H. influenzae*. *Moraxella catarrhalis* is less common in otitis media of the elderly as compared to children. Most strains produce  $\beta$ -lactamase and are resistant to penicillin G, ampicillin, and amoxicillin. Viruses isolated from patients with acute otitis media include respiratory syncytial virus, influenza virus, enteroviruses, and rhinoviruses. The most commonly identified pathogenic bacteria in chronic otitis media is *P. aeruginosa* with the next most prevalent being *S. aureus*. Methicillin-resistant strains of *S. aureus* have emerged as significant pathogens in the community. Uncommon varieties of otitis include tuberculous otitis, otitis due to *Mycobacterium chelonae*, or Wegener's granulomatosis.

### ***Clinical Manifestations***

Diagnostic criteria for acute otitis media include rapid onset of symptoms, middle ear effusion, and symptoms and signs of middle ear inflammation. The elderly with acute otitis media may present with ear pain, ear drainage, or hearing loss. Vertigo, nystagmus, and tinnitus may occur at times. Other nonspecific manifestations include fever and lethargy. On examination, the tympanic membrane may be erythematous and obliteration of its landmarks may occur due to its inflammation

and the fluid in the middle ear. Perforation of the tympanic membrane is frequent but usually not a serious complication. With proper treatment, most perforations heal uneventfully within a couple of weeks. Despite effective antimicrobial therapy, the middle ear fluid may resolve rather slowly. Serous otitis media may cause mild discomfort, but, when bilateral, the patient may complain of significant hearing loss. Cholesteatoma is a complication that can lead to bony erosion and requires surgical management. Mastoiditis, a rare complication of otitis media, should be suspected in the presence of mastoid tenderness or edema. Intracranial complications such as epidural abscess or lateral sinus thrombosis are noted uncommonly (24).

### ***Diagnostic Tests***

The presence of middle ear fluid, the hallmark of otitis media, can be ascertained by several tests. Fluid or high negative pressure in the middle ear dampens the mobility of the tympanic membrane, a useful sign demonstrated by pneumatic otoscopy. Tympanometry, a technique using an electroacoustic impedance bridge to record compliance of the tympanic membrane and middle ear pressure, presents objective evidence of the status of the middle ear and the presence or absence of fluid. In adults with otitis media with effusion, multifrequency tympanometry may be a more sensitive and objective diagnostic tool (25). Acoustic reflectometry measures sound reflectivity from the middle ear and are able to distinguish an air or fluid-filled space.

There are no diagnostic laboratory tests. The white cell count may be elevated non-specifically. A blood culture is positive in only about 3% of febrile patients with acute otitis media but, if the patient is toxic, it should be performed. Needle aspiration of the middle ear effusion (tympanocentesis) to define the microbiology should be considered in selected patients who include the critically ill, those not responding to initial antimicrobial therapy in 48–72 h, and patients with altered host defenses. Imaging studies are not routinely useful for the evaluation of acute otitis media but, in patients suspected to have complicating mastoiditis, radiographs of the mastoid air cells may be helpful.

### ***Treatment***

Antibiotic therapy of acute otitis media must be initiated without the knowledge of the exact organism and therefore must be aimed at *S. pneumoniae* and *H. influenzae*, organisms that are responsible for the vast majority of cases. Organisms recovered less frequently in otitis media of the elderly (e.g., *M. catarrhalis*, Group A streptococcus, and *S. aureus*) need not be considered in the initial therapeutic decision. However, in the immunocompromised hosts, gram-negative enteric bacilli must be considered. Commonly prescribed antibiotic therapy is listed in Table 3

**Table 3** Antibiotic therapy of acute otitis media

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Initial therapy

- Amoxicillin, 80–90 mg/kg qd (up to 2 g) PO in divided doses (bid or tid)
- Cefdinir, 14 mg/kg qd PO in 1 dose or divided doses bid
- Cefuroxime, 30 mg/kg qd PO in divided doses bid
- Azithromycin, 10 mg/kg qd PO on day 1 followed by 5 mg/kg qd PO for 4 days

Exposure to antibiotics within 30 days or treatment failure

- Amoxicillin, 90 mg/kg (up to 2 g) qd PO in divided doses (bid), plus clavulanate 6.4 mg/kg qd PO in divided doses bid
- Ceftriaxone, 50 mg/kg (maximum dose 1,000 mg) IV/IM qd for 3 days
- Clindamycin, 30–40 mg/kg qd PO in divided doses tid

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*qd* once daily; *bid* twice a day; *tid* 3 times a day; *po* orally; *IV* intravenous; *IM* intramuscular

The current drug of choice for initial therapy is a high-dose amoxicillin (80–90 mg/kg/day divided twice daily). The current incidence of ampicillin-resistant *H. influenzae* and *M. catarrhalis* in acute otitis media of the elderly is not high enough to require a change in this recommendation. With appropriate antimicrobial therapy, most patients with acute otitis media have improved significantly within 48–72 h. For persistent or recurrent acute otitis media, therapy should be switched to  $\beta$ -lactamase stable agents such as amoxicillin/clavulanate, cefaclor, cefuroxime-axetil, cefixime, cefprozil, cefpodoxime-proxetil, and trimethoprim–sulfamethoxazole. If methicillin-resistant strain of *S. aureus* is suspected, then trimethoprim–sulfamethoxazole is a good choice for initial, empirical therapy. Treatment for a 10-day period is generally considered adequate. Clinical resolution may occur in some patients without the use of antimicrobial agents, as the contents of the middle ear are discharged through the Eustachian tube or through a spontaneous perforation of the tympanic membrane. However, to prevent the suppurative complications, acute otitis media should be treated with appropriate antimicrobial agents. Appropriate antipyretics and analgesics should be offered for symptomatic relief. Oral decongestants, antihistamines, and corticosteroids, though commonly prescribed, have no proven benefit (26).

Surgical management of the persistent effusion of the middle ear includes the use of myringotomy and the placement of tympanostomy tubes. Currently, myringotomy is recommended for the relief of intractable ear pain, hastening resolution of mastoid infection, and drainage of the persistent middle ear effusion. Tympanostomy tubes are placed in the ear for persistent middle ear effusions unresponsive to adequate medical treatment over a period of 3 months. Hearing improves dramatically after placement of the ventilating tubes. The tubes have also been of value in patients who have difficulty maintaining ambient pressure in the middle ear, which, due to barotrauma, occurs in airlines personnel. The risks inherent in the placement of tubes include the following: risks of anesthesia associated with the procedure, persistent perforation, scarring of the tympanic membrane, development of cholesteatoma, and otitis media caused by swimming with ventilating tubes in place.

## ***Prevention***

For the prevention of recurrent episodes of acute otitis media, the use of chemoprophylaxis (antimicrobial agents) and immunoprophylaxis (pneumococcal vaccine) should be considered. (27). The currently available 7-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine protect against the most common types of *S. pneumoniae* found in otitis media (28). Widespread use of conjugate pneumococcal vaccine in children has led to decreasing incidence of pneumococcal otitis media not only in children but also in adults (herd immunity). In children with recurrent middle ear infection intermittent antibiotic prophylaxis (during the period of upper respiratory tract infections) using a once-a-day regimen of amoxicillin or trimethoprim–sulfisoxazole has been shown to be protective against infection. A similar approach may be helpful in the elderly with recurrent disease.

## **Sinusitis**

Sinusitis, an infection of one or more of paranasal sinuses, usually begins as a complication of a viral upper respiratory tract infection. Since sinusitis almost always involves the nasal cavity, the term rhinosinusitis is often used. Obstruction of sinus drainage and retention of secretions are the fundamental pathogenetic events in a sinus infection. Geriatric patients may be predisposed to sinusitis by several conditions that compromise the integrity of the sinus ostia and thereby interfere with aeration of sinuses and create a closed space that is susceptible to bacterial infection. Sinusitis is therefore more likely to occur in the elderly with allergic rhinitis, nasal septal deviation, nasal fractures, nasal polyps, and nasal cavity tumors. Odontogenic sinusitis is a well-recognized condition that accounts for approximately 10–12% of cases of maxillary sinusitis. Direct spread of dental infections into the maxillary sinus is possible due to the close relationship of the maxillary posterior teeth to the maxillary sinus. Common causes of odontogenic sinusitis include dental abscess and periodontal disease, which, during tooth extraction, perforates the Schneiderian membrane leading to accidental sinus perforations. An odontogenic source should be considered in individuals with symptoms of maxillary sinusitis who have a history of odontogenic infection, dentoalveolar surgery, and periodontal surgery, or in those who have a poor response to conventional therapy of sinusitis. Sinusitis is generally subdivided into acute sinusitis (symptoms less than 3 weeks), subacute sinusitis (symptoms lasting 3 weeks to 3 months), and chronic sinusitis (symptoms lasting longer than 3 months).

## ***Epidemiology and Clinical Relevance***

Sinusitis affects one in seven adults in the United States, resulting in about 31 million individuals diagnosed each year (29). Sinusitis may be complicated by serious

intracranial suppurative complications such as meningitis, brain abscess, epidural abscess, and subdural empyema. Acute bacterial sinusitis is commonly due to *S. pneumoniae* and *H. influenzae*. Less frequently isolated organisms include *Streptococcus pyogenes*, alpha-hemolytic streptococci, *S. aureus*, and *M. catarrhalis* (30). The beta-lactamase production by most strains of *M. catarrhalis* and a variable proportion of *H. influenzae* strains may lead to the therapeutic failure of beta-lactam agents such as amoxicillin in treating sinusitis due to these organisms. In acute sinusitis, over 200 viruses associated with common cold have been implicated (31). In patients requiring long-term mechanical ventilation, sinusitis has been linked to the placement of nasogastric tubes and to nasotracheal intubation. The risk of developing bacterial sinusitis on a ventilator increases with the duration of nasal cannulation and with the size of the cannula used (32). Among patients who are ventilator-treated for  $\geq 1$  week, the occurrence of bacterial sinusitis is  $\sim 10\%$  (33). The microbiology of sinusitis in these patients is quite different from that of community-acquired sinusitis. *Staphylococcus* spp., *Pseudomonas* spp., and other nosocomial organisms are frequently isolated (33). An odontogenic infection is a polymicrobial aerobic-anaerobic infection with anaerobes outnumbering the aerobes (34). The most common isolates include anaerobic streptococci, gram-negative bacilli and Enterobacteriaceae. Chronic sinusitis is caused by *H. influenzae* (in  $\sim 60\%$ ), *S. aureus*, and anaerobes. In patients with nasal polyps and cystic fibrosis, *P. aeruginosa* may be the causative agent. In the setting of diabetes and host immunocompromise, fungal organisms such as mucor should be considered. Acute fulminant and invasive fungal sinusitis with orbital extension is challenging to manage and constitutes a true emergency.

### ***Clinical Manifestations***

Acute sinusitis is usually preceded by a viral infection of the upper respiratory tract; an estimated 0.5% of common colds evolve into acute sinusitis. No single clinical finding is predictive of acute sinusitis (35). The best clinical predictors of acute sinusitis are three symptoms (maxillary toothache, poor response to decongestants, and history of colored nasal discharge) and two signs (purulent nasal secretion and abnormal transillumination). Sinusitis should be considered when purulent nasal or pharyngeal discharge and cough persist for over a week following a cold. The elderly may complain of headache, facial pain, or tightness over the involved sinus, nasal obstruction, nasal quality of voice, and a fever. Nasal examination may reveal mucosal hyperemia and mucopurulent discharge. Purulent secretion from the middle meatus is highly predictive of maxillary sinusitis. Direct inspection of the posterior pharynx or use of a pharyngeal mirror may reveal posteriorly draining purulent secretions. Tenderness over the maxillae or the frontal bone may suggest an underlying sinusitis that occurs much less commonly. Transillumination may be used to evaluate the maxillary and frontal sinuses, but its value is controversial. In chronic sinusitis, persistent nasal drainage, postnasal drip, persistent cough, foul

**Table 4** Differential diagnosis of sinusitis in the elderly

- 
- Viral upper respiratory infection
  - Rhinitis medicamentosa (topical decongestant use)
  - Drug-induced rhinitis (e.g., reserpine, prazosin, ACE inhibitors, guanethidine, cocaine abuse, etc.)
  - Allergic rhinitis
  - Sinus tumors
  - Sarcoidosis
  - Nasal foreign body
  - Midline granuloma
  - Wegner's granulomatosis
  - Rhinoscleroma
- 

*ACE* angiotensin converting enzyme

breath, and altered taste may be noted. Neglected sinusitis may exacerbate chest disease leading to increased morbidity in the elderly (36). Sinusitis should be distinguished from several disease entities such as those listed in Table 4

### ***Diagnostic Tests***

Radiologic studies are not routinely performed for the evaluation of sinus infection. Basic radiographic examination of the paranasal sinuses includes four views: (1) the Waters view (occipitontental) used to evaluate the maxillary sinuses, (2) the Caldwell view (angled posteroanterior) used to evaluate the ethmoid and frontal sinuses, (3) the lateral view used to evaluate the sphenoid sinuses and to confirm disease in the paired maxillary, ethmoid, and frontal sinuses, and (4) the submentovertex view used to evaluate the sphenoid and ethmoid sinuses. This last view is also useful for examining the lateral walls of the maxillary sinuses. In order to evaluate air fluid levels, all radiographs are done with the patient erect. Since sinusitis involves the maxillary sinuses in ~90% of cases, most cases of sinusitis would be diagnosed using only the Waters view. Radiographic evidence of acute sinusitis consists of sinus opacification, mucosal thickening of >5 mm, and the presence of air fluid level in the affected sinus. Computerized tomography is more sensitive than sinus radiography for evaluating sinus disease and is particularly helpful in delineating the osteomeatal complex (37). CT scanning is particularly useful for detecting sinus abnormalities in the sphenoid and ethmoid sinuses. However, due to its cost and poor specificity (~60%) CT scanning of sinuses is not indicated for patients with uncomplicated acute bacterial sinusitis. In one study, 40% of asymptomatic patients and 87% of patients with colds had sinus abnormalities on CT scanning (38). This study should be reserved for patients with recurrent disease, orbital or central nervous system complications, or when, due to a protracted sinus disease, surgical intervention is contemplated. An MRI may be helpful in select patients for distinguishing soft tissue tumors from inflammatory lesions.

Surface colonization of the nasal passage makes the nasal pus or the sinus exudate, obtained by rinsing through the natural sinus ostium, unsuitable for microbiologic diagnosis. Sinus puncture and quantitative cultures of the aspirated exudates remain the gold standard for reliable microbiologic diagnosis. However, such a procedure is not performed in an average case due to its invasive nature and the rather predictable bacteriology of acute sinusitis. Sinus puncture is reserved for patients with unusually severe disease, with those responding inadequately to medical therapy, or with those suspected of having intracranial extension, and also when sinusitis occurs in an immunocompromised individual.

## ***Treatment***

The management of sinusitis has been recently reviewed (29, 39, 40). Distinction between viral and bacterial etiology of acute sinusitis is difficult on clinical grounds. Bacterial etiology should be considered if symptoms or signs of acute rhinosinusitis are present for 10 days or more beyond the onset of upper respiratory symptoms, or if symptoms or signs of acute rhinosinusitis worsen within 10 days after an initial improvement.

The management of acute sinusitis should include an assessment of pain, with analgesic treatment based on the severity of pain. If a decision is made to treat for presumed bacterial sinusitis, then antimicrobial therapy is directed at *S. pneumoniae* and *H. influenzae*. Amoxicillin is recommended as first-line therapy for most adults. Quinolones with poor activity against *S. pneumoniae* (e.g., ciprofloxacin) should not be used for therapy of acute sinusitis. A recent meta-analysis for the treatment of acute bacterial sinusitis found that newer fluoroquinolones (moxifloxacin, levofloxacin, and gatifloxacin) confer no benefit over beta-lactam antibiotics (41). The commonly prescribed antimicrobial agents and their recommended dosages are listed in Table 5. The antibiotic therapy is generally administered for 10–14 days. If the patient worsens or fails to improve with the initial management option by 7 days, then the clinician should exclude other causes of illness and

**Table 5** Antimicrobial therapy of acute sinusitis in the elderly

Antimicrobial agent	Commonly used dose
Amoxicillin	500 mg q6h
Ampicillin	500 mg q8h
Amoxicillin–clavulanate	500/125 mg q8h
Trimethoprim–sulfamethoxazole	160 mg/800 mg bid
Cefaclor	500 mg q6h
Cefuroxime axetil	250 mg q12h
Clarithromycin	500 mg q12h
Azithromycin	500 mg day 1, and 250 mg qd, day 2–5
Levofloxacin	500 mg qd

*bid* twice a day; *qd* once daily



evaluate the patient for complications. Acute sinusitis should be distinguished from chronic rhinosinusitis, recurrent acute rhinosinusitis, and other causes of sinonasal symptoms. Patients with chronic rhinosinusitis and recurrent acute rhinosinusitis should be evaluated for allergic rhinitis, cystic fibrosis, immunocompromised state, ciliary dyskinesia, and anatomic variations.

Fungal sinusitis, due to mucor, requires aggressive surgical debridement and appropriate antifungal therapy similar to that of lipid formulations of amphotericin B for cure. Invasive *Aspergillus* sinusitis also typically requires extensive surgical debridement along with antifungal therapy such as that with intravenous amphotericin B. Caspofungin and voriconazole have been used with success in isolated cases of *Aspergillus* sinusitis (42).

The nasal spray decongestants phenylephrine hydrochloride (0.5%) and oxymetazoline hydrochloride (0.05%) are frequently used to treat acute sinusitis, but their role has not been proven. Rebound vasodilatation may occur in patients who use such agents frequently or for longer periods. Oral decongestants (pseudoephedrine and phenylpropanolamine) are alpha-adrenergic agonists that reduce nasal blood flow. Theoretically, oral preparations can penetrate the ostiomeatal complex where topical agents may not penetrate effectively. The use of oral decongestants has been shown to improve nasal patency. These agents can increase the functional diameter of the maxillary ostium. Some oral decongestants are available in combination with mucoevacuants, which may help to thin secretions and facilitate drainage. The antihistamines have not proven to be effective in the management of acute sinusitis. Their use may be counterproductive as the dryness of mucous membranes caused through their anticholinergic action may interfere with the clearance of purulent mucous secretions. Topical glucocorticosteroid preparations have not shown convincing benefit in the treatment of sinusitis.

Surgery may be necessary to facilitate drainage of the involved sinus and to remove the diseased mucosa. In acute bacterial sinusitis, surgical intervention is reserved because of its complications or lack of appropriate response to medical therapy. Functional endoscopic sinus surgery has revolutionized the surgical approach to sinus disease. With this approach, the affected tissue is removed and the normal tissue is left in place. Functional endoscopic sinus surgery can surgically correct anatomic obstructions and has been shown, in 80–90% of patients, to result in moderate to complete relief of symptoms. The management of odontogenic sinusitis includes a 3- to 4-week course of antimicrobials that are effective against the oral flora, surgical drainage when indicated, and treatment to remove the offending dental etiology such as an odontogenic foreign body. Surgical management of oroantral communication is indicated to reduce the likelihood of causing chronic sinus disease.

## **Prevention**

Annual vaccination against influenza and pneumococcal vaccine, aggressive management of upper respiratory infections, and the prevention or treatment of upper respiratory allergies may reduce the incidence of sinusitis in the elderly.

A high index of suspicion of sinusitis and its prompt therapy may prevent complications. Corrective surgery for nasal abnormalities to establish sinus drainage reduces the risk of sinusitis. Good dental hygiene and prompt treatment of maxillary tooth root infection will prevent the onset of maxillary sinusitis as its complication.

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# Prosthetic Joint Infections in Elderly Patients

Camelia E Marculescu, Elie F. Berbari, and Douglas R. Osmon

## Key Points

- Although prosthetic joint infections (PJIs) occur in a small proportion of patients following total joint arthroplasty, they have catastrophic consequences on morbidity and joint function and carry a high economic burden in the elderly patients.
- Clinical presentation of prosthetic joint infection is highly variable, and differentiating a painful joint arthroplasty secondary to mechanical loosening from an indolent infection can be difficult.
- There is no “gold standard” for diagnosis of a prosthetic joint infection. The diagnosis may be challenging, and current definitions used by clinicians are derived from multiple sources of information.
- The management of prosthetic joint infection is complex. The goals of therapy are to cure or control the infection, prevent its recurrence, improve or preserve functional status and reduce the risk of death.
- Multiple surgeries and prolonged course of antimicrobial therapy may be needed to accomplish these treatment goals. Close collaboration between the orthopedic surgeon and the Infectious Diseases specialist is essential for achieving those goals.

## Epidemiology and Clinical Relevance

The number of prosthetic joint infections (PJIs) in the United States population is rising because of aging and the increasing number of adults undergoing total joint replacement. In the United States, more than 500,000 primary arthroplasties are done annually and more than 1.3 million people live with a joint arthroplasty (1). It is anticipated that by 2030 more than 4 million primary total hip arthroplasty

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(THA) and total knee arthroplasty (TKA) replacements will be done per year in the United States (2). Patients 65 years and older represent approximately 60% of the patients treated with total hip replacement while 5% are more than 85 years old. Moreover, 17% of patients undergoing total hip replacement have three or more comorbidities such as congestive heart failure, chronic pulmonary disease or diabetes mellitus (3). Despite advances in prevention and treatment of PJIs, the absolute number of patients with such infections is increasing due to a lifelong risk of infection (4). Infection represents the most devastating complication following joint arthroplasty, resulting in pain, poor functional outcome, reoperations, potential loss of the arthroplasty, amputation or death. In addition, PJI is an economic burden, with an estimated cost of treating a PJI \$50,000–\$60,000 (5). The risk of infection is higher TKA (1–2%) than for THA (0.3–1.3%) or shoulder arthroplasty (less than 1%) (6–8). The infection risk is higher following revision arthroplasty (3% for THA and 6% for TKA).

## Clinical Manifestations

The clinical presentation of patients with PJIs is highly variable; however, a consistent symptom of prosthetic joint infection is pain at the site of the prosthesis, occurring in over 90% of cases (9).

Table 1 summarizes the classification of PJI according to the route of infection and the time of symptom onset after implantation. The history and physical examination of patients with suspected PJI may be unrevealing. Well-established risk factors for PJI include postoperative surgical site infections or hematoma formation, wound healing complications, a high National Nosocomial Infections Surveillance System score, presence of malignant disease, a prior total joint arthroplasty, prior infection of the joint or adjacent bone, perioperative nonarticular infection, and rheumatoid

**Table 1** Classification of prosthetic joint infections

	Characteristics
<i>According to the Route of infection</i>	
Perioperative	Inoculation of microorganisms into the surgical wound during surgery or immediately thereafter
Hematogenous	Through blood or lymph spread from a distant focus of infection
Contiguous	Contiguous spread from an adjacent focus of infection (e.g., penetrating trauma, preexisting osteomyelitis, skin and soft tissue lesions)
<i>According to the onset of symptoms after implantation</i>	
Early infection (<3 months)	Predominantly acquired during implant surgery or the following 2–4 days and caused by highly virulent organisms (e.g. <i>Staphylococcus aureus</i> or gram-negative bacilli)
Delayed or low-grade infection (3–24 months)	Predominantly acquired during implant surgery and caused by less virulent organisms (e.g., coagulase-negative staphylococci or <i>Propionibacterium acnes</i> )
Late infection (>24 months)	Predominantly caused by hematogenous seeding from remote infections

arthritis(10, 11). Leading clinical signs of early infection are persisting local tenderness, erythema, edema, wound healing complications, hematomas and fever. In the early postoperative period, the challenge is to determine if the wound infection extends to the joint arthroplasty. Persisting or increasing joint pain or prosthesis loosening are hallmarks of a delayed infection. Systemic signs of infection may be absent. During the initial postoperative month, infection presents with acute onset of pain and effusion or wound complications. A sinus tract communicating with the joint space is a definitive sign of prosthesis infection, but is not always present.

Differentiating a painful joint arthroplasty secondary to mechanical loosening from an indolent infection can be difficult in patients that present in the 3–24 month period after reimplantation (9). In these cases laboratory testing and joint aspiration are very helpful.

Late infections, typically hematogenous, often present with acute onset of systemic and joint symptoms. The most frequent sources of hematogenous infection are skin, respiratory tract, and urinary tract infections (12–14). The first 2 years following joint replacement is the most critical period for hematogenous seeding (15).

## **Diagnostic Tests**

There is no current consensus in the orthopedic or infectious diseases communities as to what constitutes a PJI. The diagnosis of PJI is easy when there is a sinus tract communicating with a joint prosthesis, purulence present in the joint space or if multiple intraoperative cultures yield the same microorganism. The diagnosis is challenging when the presentation is with isolated joint pain, prosthesis failure or loosening (16). Because of the diagnostic difficulties, current definitions used by clinicians are derived from multiple sources of information, none of which can be relied on as a gold standard.

## ***Laboratory Studies***

The peripheral white blood cell count, erythrocyte sedimentation rate, and C-reactive protein (CRP) are commonly used as screening tests in the diagnosis of PJI. These tests, however, do not reliably predict the presence or absence of infection (17–19). In a study by Spanghehl et al., the probability of PJI, when suspected, was 83 % when both sedimentation rate and CRP were elevated. The probability of PJI increases to 89% when joint aspiration revealed a positive culture, and 93% when the sedimentation rate and CRP were elevated and pathologic evaluation of periprosthetic tissue pathology revealed acute inflammation. Conversely, none of the patients with a THA and a normal CRP, sedimentation rate, and normal aspiration were subsequently found to have a PJI (17). Both the sedimentation rate and CRP are nonspecific markers of acute inflammation and may be elevated in conditions such as rheumatoid arthritis or post surgical states. False-negative results can be seen in patients with chronic low-grade infection on suppressive antibiotics (9). Compared with the

erythrocyte sedimentation rate, the CRP is more sensitive and specific for PJI (20). The role of newer laboratory markers was recently studied in the diagnosis of PJIs. A recent study found that the CRP and interleukin 6 (IL6) had the highest sensitivity of 95%. Combining CRP and IL 6 identified all patients with deep infection of the implant, whereas procalcitonin and tumor necrosis factor were very specific (98% vs. 94%), but had a low sensitivity (33% vs. 43%) (21).

Preoperative joint aspiration is usually done as a corollary to other preoperative investigations. Aspiration of the hip joint is typically done under fluoroscopic or ultrasonographic guidance.(9) A recent study in patients with failed TKAs and without underlying inflammatory joint disease showed that synovial fluid leukocyte count and neutrophil percentage were significantly higher in those with PJI than those with aseptic failure. In this study a synovial fluid white blood cell (WBC) count of more than 17,000/mm<sup>3</sup> and greater than 65% neutrophils had sensitivities of 94% and 97%, and specificities of 88% and 98%, respectively, for infection (22). Synovial fluid analysis should be accompanied by synovial fluid culture to identify the causative microorganism.

### ***Radiologic Studies***

Plain radiographs are useful in determining if the prosthesis is loose or dislocated (Fig. 1). It can show lucencies at the bone-cement interface, bony erosions, subperiosteal bone growth (23). These findings are neither sensitive nor specific. Radionuclide imaging is the modality of choice for evaluation of a possible prosthetic joint



**Fig. 1** Chronic TKA infection with loose tibial component



infection (24). Technetium-99m bone scans and gallium citrate scans have high sensitivity in detection of PJI, but unfortunately, they are nonspecific when used alone. False-positive results are associated with aseptic loosening, fractures, heterotopic ossification, neoplastic and inflammatory conditions (25). A technetium scan can remain positive for more than 1 year after implantation or infection, especially around knee prosthesis (25). On the other hand, Indium-111(<sup>111</sup>In)-labeled WBC scans have low sensitivity (0.38–0.83) but high specificity (0.94–1.00) in diagnosing periprosthetic infections (25). Older studies have shown that combination of indium and technetium scans yielded sensitivities and specificities as high as 0.98–1.00 and 0.95–0.98, respectively (26, 27). More recent studies have demonstrated a lower accuracy of the technetium–indium combination (28). Several methods of labeling leukocytes in vivo using peptides and antigranulocyte antibodies or antibody fragments are currently under investigation (24).

The use of F-18 fluorodeoxyglucose positron emission tomography (PET) for detecting PJIs is increasingly being reported as a valuable imaging modality. This modality has a very good sensitivity, but a specificity of only 55%. It does not differentiate infection from inflammation associated with an aseptically loosened prosthesis (29). It is more accurate for THA than for TKA PJI (90% vs. 78% respectively) (30).

Computed tomography (CT) and magnetic resonance imaging (MRI) are not routinely useful for diagnosing PJI, mainly because they are limited by prosthesis-induced imaging artifacts. CT is more sensitive than plain radiography and may assist in guiding joint aspiration for leukocyte count, differential, culture and surgical planning. MRI has greater resolution of soft tissue abnormalities and anatomic detail, but it can be only performed in patients with titanium or tantalum implants (30).

Currently combined leukocyte-marrow imaging (such as <sup>111</sup>In-labeled WBC and technetium-99 sulfur colloid bone marrow imaging) represents the radionuclide imaging procedure of choice for the diagnosis of PJI (31). A negative study reduces the chance of a PJI significantly, whereas a positive test requires additional investigation.

## ***Microbiology***

More than 50% of PJI's are due to staphylococci. A microbiologic diagnosis in each specific case of PJI is important for choosing optimal antimicrobial therapy for the treatment of a PJI. Isolating the same microorganism from multiple specimens obtained either from joint aspiration or at the time of surgery, provides the most useful information. A positive culture from a joint aspiration has a sensitivity that varies between 55 and 86% and a specificity between 94 and 96% for THA and TKA PJI (17, 32). The Gram stain of synovial fluid has high specificity, but very low sensitivity between 12 and 19% (17, 33, 34) and has not been found to be useful for PJI diagnosis (35). A minimum of three intraoperative cultures should be obtained (34). The specimens sent for culture should include tissue from the joint capsule, synovial lining, curetted intramedullary material, bone-cement interface, bone fragments and samples from purulent material. Routine cultures

for aerobic and anaerobic bacteria are recommended when PJI is suspected (36). False-negative culture results occur because of prior antimicrobial therapy, elution of antimicrobial from antimicrobial-impregnated bone cement, fastidious microorganisms, prolonged transport time to the laboratory, or inappropriate culture media (4). Antimicrobial therapy should be withheld for at least 2–4 weeks before any attempt to establish a microbiologic diagnosis (37). Antimicrobial prophylaxis can be withheld until tissue specimens are obtained for culture at the time of revision arthroplasty in cases when the preoperative suspicion for infection remains high but not if it is low as this may increase the risk of surgical site infection if there is not an infection present. Special culture techniques may be needed when unusual or fastidious microorganisms are suspected and the microbiology laboratory needs to be alerted. A definitive diagnosis is made by recovering the same microorganism from either repeated joint aspirations or in three of five periprosthetic surgical specimens (32, 34, 38). Proposed criteria for future definitions of PJI include joint prosthesis dysfunction, identification of a microorganism on the prosthesis or in the periprosthetic tissue or documentation that prosthesis dysfunction is caused by the presence of a microorganism on the prosthesis (16).

Gram-positive cocci account for most cases of prosthetic joint infections. *Staphylococcus aureus* and coagulase-negative staphylococci are the most common reported microorganisms in both early and late infections following joint arthroplasty (9). Except when *S. aureus* is isolated, cultures of superficial wounds or sinus tracts do not correlate reliably with deep periprosthetic cultures, because of bacterial colonization of the surrounding skin (39).

Molecular tools are attractive for the diagnosis of PJI in cases of culture-negative infection or fastidious microorganisms. Broad range polymerase chain reaction (PCR) amplification of conserved bacterial deoxyribonucleic acid sequences (e.g., 16S ribosomal RNA gene) followed by direct sequencing of the amplified product (i.e., for species determination) is a powerful technique that permits rapid detection and amplification of bacteria (1, 30, 40). This approach may be associated with false-positive results. In addition, with some exceptions (such as methicillin-resistance in *S. aureus* attributable to the presence of *mec A*), amplification techniques fail to provide antimicrobial susceptibility (1).

### ***Sonication of Prosthesis***

Organisms associated with prosthetic-joint infection form a biofilm on the surface of the prosthesis. Trampuz et al. used sonication to dislodge adherent bacteria from explanted prosthesis and performed a study to determine whether this approach would improve the diagnosis of prosthetic joint infection (41). With the use of standardized nonmicrobiologic criteria to define prosthetic-joint infection, they found that the sensitivities of periprosthetic-tissue and sonicate-fluid cultures were 60.8% and 78.5% ( $P < 0.001$ ), respectively, and the specificities were 99.2% and 98.8%, respectively. In addition, in patients receiving antimicrobial therapy within

14 days before surgery, the sensitivities of periprosthetic tissue and sonicate fluid culture were 45.0% and 75.0% ( $P < 0.001$ ), respectively. The authors concluded that culture of samples obtained by sonication of prostheses was more sensitive than conventional periprosthetic-tissue culture for the microbiologic diagnosis of prosthetic hip and knee infection, especially in patients who had received antimicrobial therapy within 14 days before surgery (41). The technique is not validated for the isolation of fungal and mycobacterial organisms and if these pathogens are suspected tissue samples should be cultured appropriately for these pathogens

### ***Histopathology***

Histopathologic evaluation of periprosthetic tissue samples from intraoperative frozen sections or permanently fixed sections is an important tool for diagnosis of PJI. The accuracy of this technique depends on the experience of histopathologist and the sampling of specimens. Because there is considerable variation in the degree of inflammation within the tissues, samples from multiple areas should be obtained, including from bone-cement or prosthesis-bone interface(9, 30). Criteria for defining a positive histopathologic result are not well defined. The finding of at least five polymorphonuclear leukocytes per high power field on frozen section has a sensitivity between 82 and 84% and a specificity of 93–96% for infection (42, 43). A higher cutoff value of 10 polymorphonuclear leukocytes per high power field significantly increases the positive predictive value of the frozen sections from 70 to 89% (42).

### **Treatment**

The management of prosthetic joint infection is challenging. The goals of therapy are to cure or control the infection, prevent its recurrence, improve or preserve functional status, and reduce the risk of death. These goals are typically accomplished by multiple surgeries and prolonged course of antimicrobial therapy. Close collaboration between the orthopedic surgeon and the infectious diseases specialist is essential for achieving those goals.

### ***Surgical Treatment***

Surgical procedures commonly used for treatment of PJI include resection arthroplasty with reimplantation at the time of resection (one-stage exchange) or at a later time (two-stage exchange); debridement and retention of prosthesis; definitive resection arthroplasty with or without arthrodesis; and amputation (9). Based on in vitro experiments and animal models, an algorithm for an individual

treatment approach was developed by Zimmerli et al. and validated in cohort studies with an overall success rate of more than 80% (4, 44). This algorithm includes four surgical treatment modalities based on the type or pathogen, duration of symptoms, stability of the implant and condition of soft tissues (4).

### **Debridement with Retention of Prosthesis**

This involves debridement of infected tissues, exchange of polyethylene components, and large volume irrigation followed by antimicrobial therapy. This limited procedure preserves both the prosthesis and bone stock (45), but carries the risk of leaving an infected foreign body in place. This modality may be suited for elderly patients with streptococcal or staphylococcal PJI and a well-fixed implant (45). Patients with early or late acute-onset hematogenous infection have typically been thought to be candidates for such a procedure. Based on the algorithm described by Zimmerli et al., debridement and retention of prosthesis is a reasonable option if the duration of symptoms is less than 3 weeks, the implant is stable, soft tissue envelope is intact, there is no sinus tract present, and an agent with activity against biofilm microorganisms is available (4, 44). This approach can have a success rate of more than 70% if the above conditions are fulfilled (4, 44, 46). Reported failure rates for this surgical modality vary between 14 and 86%, but many of these studies did not follow the algorithm described by Zimmerli which may explain some of the reported low success rates (19, 46–61).

### **One-Stage (Direct) Exchange**

This procedure includes the removal and implantation of a new prosthesis during the same surgical procedure. Data on success rates in one-stage exchange arthroplasty are mostly available for THA infection as there is significantly less data for TKA infections (75–100%) (62–71). These studies need to be interpreted with caution, since most included small number of selected patients with variable duration of follow-up. The advantages of one-stage exchange include a single procedure, lower cost, and earlier mobility. However, it also carries the risk of reinfection of newly reimplanted prosthesis by residual infection. This procedure is suitable for patients with intact soft tissue envelope, infection with low virulence microorganisms which are highly susceptible to antimicrobial agents, when there is no sinus tract formation, and when a bone graft is not necessary. Prolonged antimicrobial therapy is provided following surgery (72, 73). According to some authors, if resistant or difficult to treat microorganisms are causing the infection, such as methicillin-resistant *S. aureus* (MRSA), small-colony variants of staphylococci, enterococci, quinolone-resistant *Pseudomonas aeruginosa* or fungi, a two-stage exchange procedure is preferred (73).

### Two-Stage (Staged) Exchange

This procedure entails removal of the prosthesis and any bone cement with debridement of all infected tissue followed by administration of systemic antimicrobial therapy, and subsequent delayed reimplantation of a new prosthesis. A temporary antibiotic impregnated spacer is often implanted at the first surgery (Fig. 2). Having an adequate bone stock and a good medical fitness are prerequisites for a two-stage exchange procedure. The time interval between the two surgical procedures is variable. According to some authors, if easy-to-treat microorganisms are isolated, a short interval (2–4 weeks) and a temporary antimicrobial impregnated spacer may be used (73). If difficult-to-treat microorganisms are isolated, a longer interval (e.g., 8 weeks) without a spacer is preferred (73). Other investigators would always use a longer interval between resection and reimplantation and use a spacer when safe and effective antimicrobials can be incorporated into the spacer. Confirmation of successful eradication of infection is usually required before implantation of a new prosthesis. Typically this requires stopping the antimicrobial therapy several days to weeks before anticipated reimplantation, followed by repeat joint aspiration with cultures, or biopsies with cultures and histopathology obtained either at the time of reimplantation or as a separate surgery, i.e., three-stage procedure (9). Two-stage exchange is the standard in the treatment of TKA PJIs and chronic THA PJIs. According to a review of studies totaling 1,077 infected joint prosthesis treated with two-stage exchange, the success rate of this procedure was 87% (9), whereas studies on uncemented revision arthroplasties for THA infections showed a 92% success rate



**Fig. 2** TKA infection with temporary antibiotic impregnated spacer in place following resection arthroplasty

(74, 75). Outcome of infections involving a TKA is worsened by a premature reimplantation. Early reimplantation (within 2 weeks from removal of prosthesis) was successful only in 35% of patients with a TKA PJI (76), whereas the best outcomes were obtained in patients with infection following a primary TKA (92%) (77), and when antimicrobial-impregnated cement was used at the time of revision surgery (78). The outcome of infection following TKA can be improved by identifying patients with persistent infection prior to reimplantation by avoiding or delaying reimplantation in such patients (79). While the two-stage exchange provides the highest rate of cure in prosthetic joint infections, it also has the disadvantage of morbidity associated with multiple surgical procedures, loss of bone stock, and prolonged immobilization. Although not evaluated in randomized clinical trials, the use of antimicrobial-loaded bone cement for reimplant fixation and spacers is standard of care for treatment and prevention of prosthetic joint infections and Food and Drug Administration (FDA)-approved formulations are available. The most common antimicrobial agents loaded into polymethylmethacrylate (PMMA) are aminoglycosides (80) and vancomycin (81). These agents have been well studied for compatibility with PMMA, presumably because of their spectrum and low risk of associated allergic reactions. Emergence of antimicrobial resistance, although a rare phenomena among organisms causing prosthetic joint infections threatens the effectiveness of antimicrobial impregnated PMMA.(82) A recent study showed that other antimicrobials such as cefazolin, ciprofloxacin, gatifloxacin, linezolid, and rifampin may also be suitable for incorporation into PMMA for management of orthopedic infections (83). Cementless fixation has the advantages of preserving bone stock and avoidance of the use of foreign material that may have a deleterious effect on the immune system (9).

### **Resection Arthroplasty**

Resection arthroplasty entails the definitive removal of all prosthetic components without subsequent reimplantation. Resection arthroplasty is followed by a course of 4–6 weeks of intravenous antimicrobial therapy. Successful eradication of infection can be achieved in 60–100% of THA PJIs (84–88) and about 89% of TKA PJIs (89). This procedure is suitable for patients with poor bone stock, recurrent infections, or comorbid conditions that precluding major surgery (90) or in elderly, nonambulatory patients (9).

### **Arthrodesis (Ankylosis of the Joint)**

Arthrodesis is used when subsequent joint reimplantation is not feasible because of poor bone stock or recurrent infections. Arthrodesis can be achieved with an external fixator (Ilizarov method) or intramedullary nailing (9). When successful, arthrodesis of the knee provides excellent pain relief and a stable leg (91), but has the disadvantage of limb shortening or deformity.

## Amputation

Amputation is rarely used as a last resort when other surgical treatment options have failed to control the infection or in the presence of severe vascular compromise, uncontrolled infection bone loss, or intractable pain (92, 93).

## *Antimicrobial Therapy*

The medical treatment of many musculoskeletal infections requires prolonged systemic antimicrobial therapy, much of which is administered outside the hospital.

### Selection of Antimicrobial Therapy

In general, empirical antimicrobial therapy for chronic infections should be withheld at least 10–14 days prior to culture ascertainment at the time of surgical debridement, to ensure an adequate growth of microorganisms. The presence of concomitant soft tissue infection, bacteremia or hemodynamic instability are typical exceptions to that rule. If antimicrobials need to be started urgently in a patient with a possible PJI, obtaining blood cultures, and if possible, aspiration of any infected material should be done urgently, and empirical antimicrobial therapy should be initiated. The most efficacious antimicrobial should be chosen after consideration of the microorganism(s) causing infection and the results of any in vitro susceptibility tests and the clinical circumstances of the patient including comorbidities, antimicrobial allergies and intolerances, renal and hepatic function, and available clinical data or experience supporting the use of the particular antimicrobial (94). Suggested regimens for common microorganisms are summarized in Table 2.

A parenteral antistaphylococcal penicillin or first-generation cephalosporins are currently the drugs of choice for the treatment of methicillin-susceptible *S. aureus* (MSSA) PJIs. Some investigators would use ceftriaxone for methicillin-susceptible staphylococcal PJI but that has not been the practice of the authors to date except when the organism is penicillin susceptible. Vancomycin is the alternative agent for patients with severe type I  $\beta$ -lactam allergy, manifested by laryngeal edema, immediate urticaria or bronchospasm. Vancomycin is inferior to nafcillin or cefazolin for methicillin-susceptible staphylococci, and should not be used as first choice for such infections. A rifampin containing regimen plays a role in the treatment of staphylococcal PJI.

Rifampin has bactericidal activity against surface-adhering, slow-growing, and biofilm producing microorganisms. Its activity against staphylococci has been tested in vitro, in animal models and in clinical studies (4, 95, 96). Zimmerli et al. randomized 33 patients with staphylococcal PJI who underwent debridement and retention of the bone a joint hardware who had a infection of a stable hardware to 3–6 months of oral treatment with ciprofloxacin plus rifampin or ciprofloxacin

**Table 2** Suggested antimicrobial therapy for selected microorganisms in adults<sup>a</sup>

Microorganism	First choice	Alternative or second line
<i>Staphylococcus</i> spp. Methicillin-susceptible	Nafcillin sodium 1.5–2 g IV q 4 h or Cefazolin, 1–2 g IV q 8 h	Vancomycin 15 mg/kg IV q 12 h  or Levofloxacin, 500–750 mg PO or IV q 24 h + rifampin, 300–450 mg po q 12 h <sup>b</sup>
<i>Staphylococcus</i> spp. Methicillin-resistant	Vancomycin, 15 mg/kg IV q 12 h	Linezolid, 600 mg PO or IV q 12 h or Levofloxacin, 500–750 mg PO or IV q 24 h + rifampin, 300–450 mg po q 12 h <sup>b</sup>
<i>Enterococcus</i> spp. penicillin-susceptible <sup>c</sup>	Aqueous crystalline penicillin G, 20–24 million units IV q 24 h continuously or in six divided doses or Ampicillin sodium, 12 g IV q 24 h continuously or in six divided doses	Vancomycin, 15 mg/kg IV q12 h
<i>Enterococcus</i> spp. penicillin-resistant <sup>c</sup>	Vancomycin, 15 mg/kg IV q12 h	Linezolid, 600 mg PO or IV q 12 h
<i>Pseudomonas aeruginosa</i> <sup>d</sup>	Cefepime, 1–2 g IV q 12 h or Meropenem, 1 g IV q 8 h or Imipenem, 500 mg IV q 6–8 h	Ciprofloxacin, 750 mg PO or 400 mg IV q 12 h or Ceftazidime, 2 g IV q 8 h
<i>Enterobacter</i> spp.	Meropenem, 1 g IV q 8 h or Imipenem, 500 mg IV q 6–8 h	Cefepime, 1–2 g IV q 12 h or Ciprofloxacin, 750 mg PO or 400 mg IV q 12 h
β-hemolytic streptococci	Aqueous crystalline penicillin G, 20–24 million units IV q 24 h by continuous infusion or in six divided doses or Ceftriaxone, 1–2 g IV q 24 h	Vancomycin, 15 mg/kg IV q 12 h
<i>Propionibacterium acnes</i> and <i>Corynebacterium</i> spp.	Aqueous crystalline penicillin G, 20–24 IV q 24 h by continuous infusion or in six divided doses or Ceftriaxone 1–2 g IV q 24 h or Vancomycin, 15 mg/kg IV q 12 h	Clindamycin, 600–900 mg IV q 8 h

Modified with permission from (9)

<sup>a</sup>Dose based on normal renal and hepatic function may need to be adjusted if renal or hepatic impairment exists. Recommendations assume in vitro susceptibility and no allergies exists.

<sup>b</sup>Levofloxacin–rifampin combination therapy for patients managed by debridement with retention. If organism susceptible to levofloxacin, co-trimoxazole or minocycline may be substituted. Rifampin would also be used in combination with the intravenous therapy as well if treating a PJI that has been managed with debridement and retention.

<sup>c</sup>Addition of aminoglycoside for bactericidal synergy is optional. Considerations in choice of an agent are similar to those noted for treatment of enterococcal endocarditis.

<sup>d</sup>Addition of an aminoglycoside is optional.



alone, after initial therapy with intravenous flucloxacillin or vancomycin in lieu of ciprofloxacin. All 12 patients treated with a rifampin-containing regimen and 58% of the 22 who did not receive rifampin were cured without removal of the device (46). Rifampin use is limited by its side effects, especially gastrointestinal, and its potential for drug–drug interactions. Rifampin should not be used as monotherapy due to the potential rapid development of resistance.

Recent data suggests that prosthetic joint infections due to MRSA may have a worse outcome than of MSSA (97). Vancomycin has been traditionally the drug of choice to treat such infections. However, the clinical success rate with vancomycin for MRSA PJI is low and inversely correlated with vancomycin minimum inhibitory concentration (98). Alternative therapies to vancomycin for treatment of MRSA infections include linezolid, daptomycin, teicoplanin, trimethoprim–sulfamethoxazole, quinupristin–dalfopristin or tigecycline.

Linezolid seems promising for the treatment of staphylococcal osteomyelitis (99–101), however long-term administration is problematic due to its side effects, in particular bone marrow suppression and neuropathy (100). Daptomycin is a cyclic lipopeptide antibiotic rapidly bactericidal *in vitro* against a broad spectrum of gram-positive bacteria, including MRSA. Experimental model of osteomyelitis showed encouraging results in eradication of MRSA from infected bone (100). Data on the use of daptomycin in retrospective cohorts are conflicting (102, 103). Studies are on their way for its further evaluation in prosthetic joint infections. Tigecycline is a tetracycline-like bacteriostatic antibiotic that has higher concentration in the infected bone than in non-infected bone. Experimental studies with tigecycline in MRSA osteomyelitis seem to be promising but clinical data are very limited.(104) Tigecycline, linezolid and daptomycin are not FDA approved for the treatment of bone and joint infections.

## **Oral Antimicrobial Therapy**

Certain antimicrobials when administered orally can achieve similar serum and bone levels when compared with parenteral administration. The authors use selected oral antimicrobials with excellent bioavailability (drugs that achieve similar serum or tissue concentrations whether given orally or intravenously) whenever possible in compliant patients with a functional gastrointestinal tract. Examples of highly bioavailable oral antimicrobial therapy include linezolid, co-trimoxazole, fluoroquinolones, metronidazole and azole antifungal agents.

## **Chronic Oral Antimicrobial Suppression**

The recommendation for the use of chronic oral antimicrobial suppression is based on expert’s opinion and small cohort studies (50, 55, 56, 105), rather than randomized clinical trials. In many patients treated successfully with debridement and retention of the prosthesis, long-term suppressive antimicrobials is often recommended

(51, 55, 105, 106). Indication for this approach may include situations where surgery is not feasible due to poor health, well-fixed prosthesis that is difficult to remove, unacceptable functional results from removal of the prosthesis, or patient's refusal for further surgical procedures (9). The goals of long-term antimicrobial suppression are to provide symptomatic relief, maintain a functional joint and prevent the systemic spread of the infection. There are certain prerequisites for a successful outcome when using chronic oral suppression, such as lack of systemic infection, infection with a highly susceptible microorganism, availability of oral antimicrobials to which the microorganism is susceptible, patient's compliance and tolerability, drug–drug interactions, presence of a well-fixed and functional prosthesis. Even with these criteria met, the success is variable, and varies between 23 and 86%, depending on the study design, patient's selection, microorganism, surgical therapy, and definition of success and failure (50, 55, 56, 105, 106). The ideal regimen and optimal duration of chronic oral antimicrobial suppression are not well-established and remain to be determined.

## Summary

Success in the treatment of prosthetic joint infections requires the selection of the optimal surgical approach and antimicrobial therapy. In crafting a particular therapeutic plan one must take into consideration the type of organism, symptoms duration, joint age, status of the soft tissue envelope, condition of the bone stock, the virulence and antimicrobial susceptibilities of the microorganism, side effects of antimicrobial therapy, alternative options, and condition of the host. A close cooperation with the infectious diseases specialist and the orthopedic surgeon are prerequisites for a successful outcome. Treatment should be individualized for a specific infection and patient.

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# Staphylococcal and Enterococcal Infections

Christopher J. Graber and Dennis R. Schaberg

## Key Points

- Staphylococci and enterococci are responsible for a large proportion of infections in elderly patients, mostly in patients who have frequent contact with the healthcare system; resistance to antibiotics among these organisms is increasing.
- Though community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) has become epidemic in the United States since 2000 and has caused MRSA to now be considered predominantly an outpatient pathogen, it has had less of an impact on the elderly than on younger adults.
- Staphylococci cause a wide spectrum of disease: skin and soft tissue, respiratory tract, bloodstream, gastrointestinal, genitourinary, and prosthetic device-associated disease; enterococcal disease meanwhile is largely limited to the bloodstream, genitourinary tract, and prosthetic device-associated disease.
- Several new antibiotic options are available for the treatment of resistant staphylococcal and enterococcal infections, including daptomycin, linezolid, tigecycline, and quinupristin–dalfopristin, and, in the next few years, other options (telavancin, ceftobiprole) are expected.
- Prevention of staphylococcal disease in the community setting relies on restriction of contact with and appropriate covering of skin lesions, attention to personal hygiene, elimination of potential fomites, and reducing crowded living situations when possible; meanwhile, in-hospital prevention relies on aggressive management of compromised skin integrity, aspiration precautions, proper procedural techniques, and discontinuation of invasive catheterization as early as possible. Prevention of MRSA and resistant enterococcal infection in healthcare settings focuses on eliminating cross-infection.

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## Staphylococci

### *Introduction*

Diseases caused by staphylococci are associated with significant morbidity and mortality in the elderly population. Staphylococci that cause disease in humans are usually categorized according to the presence of coagulase: the coagulase-positive *S. aureus* is the most virulent of the staphylococci and causes a wide range of disease (skin and soft tissue, respiratory tract, bloodstream, and bone and joint infections) while the coagulase-negative staphylococci (*S. epidermidis*, *S. saprophyticus*, etc.) tend to cause more indolent disease, which is largely limited to the urinary tract and bloodstream and in infections associated with intravascular devices or prosthetic materials. Methicillin-resistant *S. aureus* (MRSA) has now emerged as a significant cause of disease in the elderly population, especially in those in frequent contact with the healthcare system. Most recently, community-associated methicillin-resistant *S. aureus* (CA-MRSA) has received significant attention in the medical literature and popular press; fortunately, it has had a disproportionately lesser impact on the elderly population.

### *Epidemiology and Clinical Relevance*

#### **Frequency of Staphylococcal Colonization and Disease in the Aging**

Staphylococci are frequent colonizers of the human host. While coagulase-negative staphylococci such as *S. epidermidis* are frequently isolated from skin surfaces in normal hosts and typically do not cause disease in patients without indwelling prosthetic devices, most *S. aureus* infections occur in those who are previously colonized (1); however, CA-MRSA infection may be an exception to this paradigm (discussed below). While *S. aureus* also typically colonizes skin surfaces, particularly in the perineal or axillary regions, its primary site of colonization is the anterior nares.

It is estimated that approximately 30% of the population of the United States is colonized with *S. aureus* at any particular time, with 0.8% being colonized with MRSA. While *S. aureus* colonization is only slightly less common in the elderly population as compared with the younger populations, colonization with MRSA is significantly higher in the elderly population (estimated 2.2% in the general population of those age 60 and greater) (2) and is often much higher in residents of long-term care facilities (5–34%) (3) and in patients with frequent contact with the healthcare system.

Among the elderly population, MRSA also causes a disproportionate amount of invasive disease and deaths. A Centers for Disease Control and Prevention survey of invasive MRSA disease in nine communities across the United States in 2004–2005

estimated that the overall rate of invasive MRSA disease in the general U.S. population was 31.8 cases per 100,000 population but was 127.7 cases per 100,000 in those age 65 and older (4). Over 60% of the MRSA invasive disease in this age group was seen in patients with health care-associated disease presenting in the outpatient setting; less than 10% was seen in those with no significant history of healthcare risk factors. Overall mortality associated with invasive MRSA disease was over five times higher in those age 65 and older than in the general population.

### **The Evolution of Drug Resistance in *Staphylococcus aureus* and Emergence of Community-Associated MRSA**

When penicillin was first used widely in clinical settings around 1942, staphylococci were initially universally susceptible. However, staphylococci, particularly *S. aureus*, have become increasingly resistant to penicillin and its derivatives over time. By 1944, strains of *S. aureus* producing penicillinase (and thus engendering penicillin resistance) had been reported. These strains remained largely in hospital settings until the 1970s, when they became common in the community as well.

Introduced in the 1960s were penicillinase-resistant synthetic agents such as methicillin, nafcillin, and oxacillin, and, akin to the emergence of penicillin-resistant *S. aureus*, the emergence of methicillin resistant *S. aureus* (MRSA) was almost immediate, but it was largely confined to hospital settings. Initially, MRSA was seen almost exclusively in large urban medical centers, but, by the 1990s, smaller community medical centers also started reporting increasing rates of MRSA (5). MRSA had only rarely appeared in the community setting by this time and typically in patients who had a large degree of contact with the healthcare system.

Subsequently, in the late 1990s, reports that certain MRSA strains, causing severe skin and soft tissue disease and/or pneumonia in previously healthy individuals in the community with no prior history of healthcare contact, began to surface. One of these community-associated MRSA (CA-MRSA) clones, called USA300, has become epidemic in several communities throughout the United States (6). The USA300 clone possesses a number of genetic determinants that may contribute to its rapid spread and virulence, most notably the Arginine Catabolic Mobile Element, likely acquired from *S. epidermidis* and thought to play a role in enhanced survival on skin surfaces and a number of pore-forming proteins toxic to human host defense cells such as Pantón–Valentine leukocidin and alpha-hemolysin (7). While disease caused by CA-MRSA seemed to initially be confined to distinct demographic groups (Native Americans, contact sport participants, individuals in day care centers or prisons, military personnel, men who have sex with men), a study of patients presenting with purulent skin and soft tissue infections during August 2004 at 11 nationwide university-affiliated emergency departments established the presence of *S. aureus* in 76% of those infections; MRSA accounted for 59% of the *S. aureus* isolated, almost all of which (97%) was USA300 (8). Some have suggested that the pathogenesis of CA-MRSA relies more upon direct skin-to-skin contact with an infected individual rather than the typical paradigm of

*S. aureus* colonization progressing to disease; however, though more research is needed to answer this question (9).

### **The Impact of CA-MRSA on the Aging: A Community-Wide Case Study**

The patients in the emergency department study were relatively young (median age 39 years), suggesting that the impact of CA-MRSA epidemic on older individuals is less than that of younger individuals (8). Another study that examined the annual incidence of MRSA disease across nine of the 10 medical centers and their affiliated outpatient clinics in and immediately around San Francisco in 2004–2005 (10) demonstrated that the highest incidence of community-onset infections among San Francisco residents was in the 35–44-year-old age group (430 cases per 100,000 residents); there was a progressive decrease incidence among older age groups until, those 85 years old and above (425 cases per 100,000 residents), revealed a spike upwards in community-onset infections. Most of the patients in this age group, however, had frequent contact with the healthcare system and were more likely to present with infections caused by MRSA strains that were from hospital-associated genotypic lineages. Hospital-onset MRSA infections continued to impact the elderly population the greatest in this study, with an annual incidence increasing from 15 cases per 100,000 residents in those age 35–44 to 135 cases per 100,000 residents in those age 85 and above. However, even among the older age groups, the vast majority of MRSA disease was acquired in the community setting, representing a paradigm shift away from MRSA as being perceived predominantly as a hospital-associated pathogen. Also, the USA300 clone was a significant cause of hospital-onset disease in this study, accounting for an estimated 43% of the strains isolated in the hospital setting, though it was more likely to cause disease earlier in the hospital course than the traditional hospital-associated clones.

### **Increasing Vancomycin Resistance in *Staphylococcus aureus***

While penicillin and methicillin resistance developed rapidly in *S. aureus*, vancomycin resistance has been very slow to emerge. Despite the introduction of vancomycin in 1956, intermediate resistance to vancomycin (VISA) was not seen in *S. aureus* until the late 1990s, and frank vancomycin resistance (VRSA), in which *S. aureus* acquired the *vanA* vancomycin resistance gene from vancomycin-resistant *Enterococcus*, was not seen until 2002. Only seven cases of VRSA have been reported, most commonly in indolent skin and soft tissue disease and with patients who have heavy contact with the healthcare system. Since the 1990s, however, there have been an increasing number of clinical failures of vancomycin therapy associated with *S. aureus* isolates; these failures display moderate elevations in vancomycin minimum inhibitory concentration and can thus survive in the presence of low concentrations of vancomycin, prompting a shift in what is considered to be reduced susceptibility to vancomycin (11) and a search for alternative agents

to vancomycin. As such isolates are often isolated from deep-seated infections that can commonly occur in elderly patients (catheter-associated bacteremia, endocarditis involving prosthetic valves, osteomyelitis, etc.) this issue is of particular concern to the geriatric care community.

## *Clinical Manifestations of Staphylococcal Disease*

### **Skin and Soft Tissue Disease**

The most common clinical condition in which staphylococci are significant causes of disease is skin and soft tissue disease, which can run the spectrum from localized superficial infections such as impetigo to life-threatening necrotizing fasciitis (12).

#### Impetigo, Erysipelas, and Cellulitis

Impetigo is characterized by discrete, superficial pustular or bullous lesions that are typically caused by *S. aureus* (including MRSA) and/or group A streptococci. While impetigo most frequently occurs in children, it can occasionally be seen in older adults.

The terms “erysipelas” and “cellulitis” are often used interchangeably, but, classically, erysipelas refers to localized infection of the upper dermis with well-demarcated erythema and edema, while cellulitis is typically described as involving the lower dermis without a sharp demarcation between infected and uninfected tissue (see also chapter “Skin and Soft Tissues Infections”).

Certain factors that are common in the aging population are risk factors for the development of cellulitis; these are the following: obesity, diabetes mellitus, previous cutaneous damage or skin infection, venous insufficiency, lymphatic obstruction, inflammatory dermatoses, and tinea pedis.

While erysipelas is usually streptococcal in origin and cellulitis is often streptococcal in origin as well, *S. aureus* has now emerged as a significant cause of cellulitis. In particular, if there is purulence associated with cellulitis, *S. aureus* is the more likely pathogen. However, it is often difficult to distinguish staphylococcal from streptococcal etiology in non-purulent erysipelas and cellulitis, as aspiration of the skin and blood cultures are rarely helpful. Epidemiologic clues may suggest non-streptococcal and non-staphylococcal etiologies of cellulitis (i.e., *Pasteurella* and *Capnocytophaga* spp. associated with cat and dog bites, *Aeromonas* and *Vibrio* spp. associated with freshwater and saltwater exposure, respectively).

#### Cutaneous Abscesses, Folliculitis, Furuncles, and Carbuncles

Cutaneous abscesses are collections of pus that arise within the deeper structures of the skin when bacteria are introduced into these deeper layers. They may occur in

the setting of penetrating trauma to the skin but can also occur without any apparent inciting event, particularly when they are caused by CA-MRSA. CA-MRSA cutaneous abscesses in particular have been described as resembling spider bites. Folliculitis is an infection of the hair follicle that is confined to the superficial layers of the skin, while furuncles (aka “boils”) are infections of hair follicles in which purulence extends down the hair follicle and into the deeper layers of the skin thereby forming a small abscess. When the infection from one furuncle extends to involve several adjacent hair follicles, it is termed a carbuncle.

Carbuncles are often seen on the back of the neck, particularly in patients with diabetes mellitus. Outbreaks of furunculosis can occur in families and other settings in which close personal contact is involved, and some individuals may have repeated attacks of furunculosis. *S. aureus* is the most frequent cause of all of the above, not only in elderly populations but also in the general population as a whole, with CA-MRSA being responsible for a rising number of cases.

### Infected Wounds: Surgical Site Infections and Pressure Ulcer Infections

Surgical site infections are a considerable source of morbidity in the aging and are the most common adverse events affecting hospitalized patients who have undergone surgery (13). Pressure ulcer infections remain a significant source of morbidity in vulnerable patients as well. Staphylococci and enterococci are frequently isolated organisms from infected wounds, though, in truly infected wounds, staphylococci (particularly *S. aureus*) are more likely to contribute to pathogenicity than are enterococci.

### Necrotizing Fasciitis

Necrotizing fasciitis is characterized by a rapidly spreading infection of the deep subcutaneous tissues, which is characterized by pain out of proportion to examination and rapidly followed by signs of severe systemic toxicity (see also chapter “Skin and Soft Tissues Infections”). Factors that may distinguish necrotizing fasciitis from simple cellulitis may include severe, constant pain, severe blistering, gas in the soft tissues that can be palpated or seen on X-ray imaging, and edema that extends beyond erythema of the affected area. Fortunately, necrotizing fasciitis caused by *S. aureus* remains rare, and even though CA-MRSA is responsible for a growing number of cases of necrotizing fasciitis, this phenomenon seems to be rather uncommon in older adults (14).

### Respiratory Tract Disease

While there have been increasing reports of severe, necrotizing CA-MRSA pneumonia in otherwise healthy hosts, most respiratory disease in the aging that is

caused by staphylococci is typically *S. aureus* pneumonia, which is acquired in the health care-associated or inpatient setting, and often in the settings of ventilator use, aspiration, or antecedent influenza infection (see also chapter “Bronchitis and Pneumonia”). A study examining the etiology of severe pneumonia in the very elderly (age 75 and older), who presented to a Buffalo, NY, hospital from either the community or from a nursing home in 1996–1999, identified *S. aureus* in 7% of community-acquired pneumonia and in 29% of nursing home-acquired pneumonia (15). *S. aureus* was the most frequently encountered pathogen in the nursing home setting. MRSA was not seen in pneumonia presenting from the community but was responsible for 21% of all *S. aureus* pneumonia presenting from the nursing home. Subsequent reports, however, point to an increasing percentage of nosocomial *S. aureus* pneumonia in the elderly being attributed to MRSA (up to 70%), though it is likely that methicillin resistance itself does not lead to worse outcomes (16).

### Urinary Tract Disease

While the vast majority of uncomplicated urinary tract infections (UTIs) in younger individuals occurs in women and is caused by *Escherichia coli*, urinary tract infections in older individuals are associated with less of a female predominance (2:1) and more frequently involve enterobacteriaceae other than *E. coli* and gram-positive pathogens such as staphylococci, group B streptococci and enterococci (see also chapter “Urinary Tract Infection”). In particular, coagulase-negative staphylococci are common causes of bacteriuria in elderly patients who have indwelling urinary catheters, often in combination with other bacteria (17), though it may often be difficult to determine whether or not their presence represents colonization or true infection (see section “Diagnosis and Treatment”).

*S. aureus* is a somewhat less frequent cause of catheter-associated UTI but is often associated with dissemination to the bloodstream and increased mortality risk (18).

### Bacteremia

Staphylococci are important causes of bacteremia in elderly individuals, and *S. aureus* is a frequent cause of endocarditis (see also chapters “Sepsis” and “Infective Endocarditis”). A prospective population-based study of bacteremia in those 65 and older from 2003 to 2005, stratified according to community-acquired, health care-associated, and nosocomial onset, demonstrated that *S. aureus* was responsible for 8%, 25%, and 24% of all the bacteremias in the three respective categories (19). MRSA was absent in community-onset bacteremia but accounted for 54% and 44% of health care-associated and nosocomial *S. aureus* bacteremia, respectively. An earlier review of all patients presenting with bacteremia from nursing homes to an urban, public, university-affiliated hospital in 1997–2000, revealed *S. aureus* in 18% of cases, of which 29% were MRSA (20). Of the 41 cases of *S. aureus* bacteremia identified, 10 (24%) were from a presumed urinary tract source, 5 (12%) were

associated with pneumonia, 1 (2%) was associated with skin and soft tissue infection, 5 (12%) were associated with other sites, and 20 (49%) had no obvious source. In patients without intravascular catheters or other indwelling prosthetic devices, coagulase-negative staphylococci are infrequent causes of true bacteremia but, in patients with artificial heart valves, are frequent causes of endocarditis.

### **Bone, Joint, and Prosthesis-Associated Disease**

*S. aureus* is a frequent cause of acute hematogenous osteomyelitis that occurs in the setting of bacteremia; it is often vertebral in location and may be associated with epidural abscess. *S. aureus* may also contribute to the often polymicrobial osteomyelitis that is frequently seen in diabetic and vascular insufficiency foot infections (21). While coagulase-negative staphylococci can also be isolated from such foot infections, they likely play a much smaller role in pathogenicity. *S. aureus* is also a frequent cause of native joint infection that may result from either hematogenous seeding or direct inoculation of the organism (see also chapter “Osteomyelitis and Septic Arthritis”).

Both *S. aureus* and coagulase-negative staphylococci are frequent causes of prosthetic joint infections; *S. aureus* typically causes prosthetic joint infections that present early following joint implantation (i.e., within 3 months) and that are characterized by acute joint pain, effusion, erythema, and fever. Coagulase-negative staphylococci are typically responsible for more indolent presentations of prosthetic joint infection that, following implantation, occur later and are typically characterized by implant loosening or persistent joint pain often in the absence of significant fever or erythema (22) (see also chapter “Prosthetic Joint Infections in Elderly Patients”).

## ***Diagnosis and Treatment***

### **General Principles in Management**

#### **Skin and Soft Tissue Staphylococcal Infections**

Treatment for localized superficial skin disease such as impetigo can often be topical (i.e., mupirocin) for limited disease, while oral or intravenous antibiotics can be used for more extensive disease. For most cases of cellulitis, especially those with evidence of purulence, empirical antistaphylococcal antibiotic coverage (including coverage for MRSA) should be given, and a culture of any purulent material present should be obtained. To promote lymphatic and venous drainage, when possible, the cellulitic limb should be elevated. Patients presenting with cellulitis should also receive appropriate therapy for conditions predisposing to cellulitis such as diabetes mellitus, tinea pedis, and venous insufficiency.

The most effective treatment for large cutaneous abscesses, furuncles, and carbuncles is incision and drainage; antibiotic therapy in patients receiving incision and drainage should be reserved for those with a large degree of surrounding inflammation, signs of systemic toxicity (fever, tachycardia, hypotension), significant comorbidities, or relative immune compromise. Folliculitis and smaller non-drainable abscesses may respond to warm compresses and a 1- to 2-week course of oral antibiotic therapy. Empirical therapy in these cases should cover the possibility of MRSA, and, when possible, cultures should be obtained in all patients in whom antibiotic therapy is planned in order to confirm that the empirical antibiotics that have been chosen are indeed appropriate. Necrotizing fasciitis and surgical site infections caused by staphylococci require prompt surgical consultation in addition to intravenous antibiotic therapy.

### Other Staphylococcal Infection

Given the high prevalence of MRSA as a causative pathogen in nursing home-acquired pneumonia and ventilator-associated infections, an antibiotic regimen that covers MRSA must be considered as part of empirical therapy in all elderly patients presenting from a nursing home with pneumonia, particularly if an aspiration episode preceded development of pneumonia or ventilator-associated pneumonia. While controversy currently exists regarding the efficacy of vancomycin in the treatment of MRSA pneumonia, it remains a front-line agent, although, despite its hematologic toxicity (discussed below) and high cost, linezolid may be a suitable alternative (23). Thorough drainage of any pleural empyema associated with *S. aureus* pneumonia is typically required, either by chest tube thoracotomy or, rarely, by surgical decortication.

As staphylococci are frequently isolated from the urine in the setting of urinary tract catheterization, it is important to distinguish between asymptomatic colonization and true infection. The presence or absence of fever, dysuria, urgency, or abdominal or flank pain may be useful clues. If staphylococci are indeed truly pathogenic, then they are typically isolated from urinary culture at an amount greater than 100,000 colony-forming units per milliliter. Whenever the diagnosis of catheter-associated UTI is made, discontinuation or changing of the catheter should be considered. Occasionally, staphylococci can seed the urine from a primary bloodstream infection; this possibility must be considered, particularly in all cases of *S. aureus* bacteriuria. The isolation of coagulase-negative staphylococci from the blood often represents blood culture contamination, particularly if the patient does not have an indwelling intravascular device or artificial heart valve. Repeating the blood cultures (ideally drawn from peripheral sites) in the setting of a single positive culture for a coagulase-negative staphylococcus will help determine whether or not that culture was a contaminant. However, *S. aureus* is rarely a blood culture contaminant, and all cases of *S. aureus* bacteremia require investigation of potential etiologies, including echocardiography (to determine whether endocarditis is present), examination of all intravascular devices, and follow-up cultures every



24–48 h to document resolution of bacteremia. The treatment of endocarditis caused by *S. aureus* and coagulase-negative staphylococci is similar and typically involves 4–6 weeks of intravenous antibiotic therapy. For intravascular catheter-associated *S. aureus* bacteremia, removal of the catheter is typically recommended along with at least 2 weeks of intravenous antibiotic therapy; in select cases, preservation of the catheter with antibiotic lock therapy can be considered.

Treatment for acute non-prosthetic-associated staphylococcal joint infection typically involves surgical drainage combined with a combination of intravenous then oral antibiotic therapy, which is typically effective; while the treatment of staphylococcal osteomyelitis is often difficult, there is a significant treatment failure rate even in the settings where adequate surgical debridement is possible. Prosthetic joint infections are treated with a combination of intravenous and oral antibiotics according to time and acuity of presentation, prosthesis retention, liner exchange, one-step prosthesis exchange, and two-step prosthesis exchange and with intervening antimicrobial-impregnated spacer placement; depending on the clinical situation, all these are appropriate options. Occasionally, other non-orthopedic indwelling prostheses can be infected with staphylococcal species (e.g., vascular grafts, pacemaker-defibrillators, ventricular assist devices, ventricular shunts); frequently, treatment of these infections is also achieved via a combined surgical and antimicrobial approach (24). For patients receiving long-term (>2 week) antibiotic therapy for deep-seated staphylococcal disease, close follow-up must be ensured in order to monitor for treatment failure (i.e., disease persistence or recurrence) and side effects associated with antibiotic therapy, as both can occur frequently, particularly in the elderly population. Depending on the antibiotic used, hematologic parameters, renal function, and liver function should be routinely monitored.

### **Antibiotics Active Against Staphylococci**

For infections caused by staphylococci that retain susceptibility to methicillin, a penicillinase-resistant penicillin (e.g., nafcillin, oxacillin, dicloxacillin), a penicillin–penicillinase inhibitor combination (e.g., ampicillin–sulbactam, amoxicillin–clavulanate) or a first-generation cephalosporin (e.g., ceftazolin, cephalexin) remain the treatment of choice. When additional gram-negative coverage is required, anti-pseudomonal penicillin–penicillinase inhibitor combinations (e.g., ticarcillin–clavulanate, piperacillin–tazobactam) and second-generation cephalosporins (e.g., ceftriaxone) also retain reasonably good anti-staphylococcal activity. Occasionally, staphylococci will be sensitive to penicillin, allowing treatment with penicillin G, penicillin V/K, ampicillin, or amoxicillin, but this susceptibility pattern is becoming increasingly uncommon.

For infections caused by methicillin-resistant staphylococci for which oral therapy is deemed appropriate, depending on the organism's resistance profile, several options are available. The vast majority of MRSA isolates are susceptible to trimethoprim–sulfamethoxazole in vitro, suggesting its use for mild to moderate

skin and soft tissue disease that is due to MRSA. However, clinical failures have been frequent when trimethoprim–sulfamethoxazole has been solely relied upon for the treatment of more invasive staphylococcal infections (25). Clindamycin can be considered for treatment of staphylococcal skin infection or pneumonia; however, clindamycin resistance is common among hospital-acquired MRSA isolates, and its common side effect of diarrhea (with or without *Clostridium difficile*-associated colitis) makes use of this agent, in the elderly, somewhat problematic. Tetracyclines such as doxycycline and minocycline can be used for mild to moderate staphylococcal skin and soft tissue disease; they are generally well-tolerated, though photosensitivity is very common. Linezolid, available in both oral and intravenous form, can be used to treat a wide spectrum of staphylococcal disease, including moderate to severe skin and soft tissue disease, pneumonia, and bone and joint infection, though hematologic toxicity (leukopenia and thrombocytopenia) and expense limit its extended use. Combination of linezolid with serotonin-specific reuptake inhibitors (SSRIs) can also uncommonly cause a “serotonin syndrome” characterized by fever, cognitive dysfunction, hyperreflexia, and incoordination that resolves upon linezolid discontinuation. Rifampin can also be considered in adjunctive therapy of infection associated with prosthetic orthopedic devices and in recurrent skin and soft tissue disease; it must never be used alone to treat any staphylococcal infection, for resistance can develop rapidly with rifampin monotherapy. Care should also be taken to review other medications the patient may be receiving, as rifampin has numerous interactions with other medications. Because resistance can emerge rapidly, quinolones are generally unreliable against *S. aureus* infections.

Recently, several antibiotics have been developed as alternatives to vancomycin for the treatment of serious infections caused by methicillin-resistant staphylococci and ampicillin-resistant enterococci; these are summarized in Table 1. Of note, linezolid and tigecycline should not be used in the treatment of bacteremia; daptomycin is ineffective in the treatment of pneumonia, and quinupristin–dalfopristin’s side effect profile and lack of efficacy vs. *E. faecalis* severely limits its use. In the next few years, newer agents with activity against resistant gram positive cocci may also become available telavancin, a lipoglycopeptide, is structurally similar to vancomycin, and ceftobiprole, an extended-spectrum cephalosporin, is active against MRSA. Aminoglycosides are also sometimes used in combination with beta-lactams or vancomycin in the treatment of staphylococcal endocarditis; because of significant ototoxicity and nephrotoxicity, when these agents are used in the elderly population, close monitoring of antibiotic levels, hearing, and renal function are required.

## ***Prevention***

### **Prevention of Community-Associated Staphylococcal Disease in the Aging**

As the majority of staphylococcal disease (including MRSA) is skin and soft tissue disease that occurs in the community setting, efforts designed to limit the spread of

**Table 1** Antibiotics recommended for serious infections caused by methicillin-resistant staphylococcus aureus and ampicillin-resistant enterococci

Antibiotic	Dosage	Route	Advantages	Disadvantages
Vancomycin	0.5–1.5 g typically q12h	IV	Extensive clinical experience, rare emergence of frank resistance seen in staphylococci	Requires dose adjustment for renal function, renal and oto-toxicity (esp. in high doses), lower efficacy vs. <i>S. aureus</i> with higher yet still “susceptible” MICs, “red man” syndrome
Linezolid	600 mg q12h	IV or po	Effective in MRSA pneumonia, extremely rare emergence of resistance seen in both staphylococci and enterococci	Unreliable for treatment of bacteremia, frequent leukopenia and thrombocytopenia, neuropathy, potential drug interactions (e.g., pseudoephedrine, SSRIs), expensive
Daptomycin	4–6 mg/kg, typically q24h	IV	Effective in bacteremia, relatively rare resistance seen in both staphylococci and enterococci	Requires dose adjustment for renal function, inactivated by pulmonary surfactant (ineffective for treatment of pneumonia), potential rhabdomyolysis
Tigecycline	100 mg loading, then 50 mg q12h	IV	No resistance reported in both staphylococci and enterococci, fairly broad gram-negative coverage as well	Does not attain adequate blood levels for treatment of bacteremia, nausea, vomiting, photosensitivity
Quinupristin–dalbopristin	75 mg/kg q8h	IV	Relatively rare resistance in both staphylococci and enterococci	No activity vs. <i>E. faecalis</i> , arthralgias and myalgias, hyperbilirubinemia, phlebitis, potential drug interactions (e.g., cyclosporine, amitodarone, benzodiazepines)

IV intravenous, po orally, MIC minimum inhibitory concentrations, MRSA methicillin-resistant *Staphylococcus aureus*, SSRIs selective serotonin receptor inhibitors

skin and soft tissue in the community are likely to achieve a greater overall impact than inpatient infection control efforts. In response to the CA-MRSA epidemic, the Centers for Disease Control and Prevention (26) have proposed at least five “C”s that represent risks for staphylococcal disease in the community; these could be targets for intervention (1) Contact (i.e., direct skin-to-skin contact); (2) cleanliness (lack of); (3) compromised skin integrity; (4) contaminated objects, surfaces, and items, and (5) crowded living conditions. Potential interventions associated with each of these risks are summarized in Table 2. While these risks may be more specific to CA-MRSA disease, where person-to-person transmission of active infection is believed to be more important than transfer of colonization, the interventions proposed are likely to reduce transmission of both active infection and colonization. In the community setting, decolonization efforts using topical and/or systemic antibiotics have been largely focused on patients presenting with recurrent staphylococcal disease, despite very little data regarding its efficacy in this situation (27). A combination of chlorhexidine body washes, intranasal mupirocin, and oral doxycycline and rifampin shows greater long-term effectiveness in eradicating MRSA colonization than most strategies, although resistance to mupirocin, which arises easily with repeated use, is associated with failure of this regimen (28).

In the hospital setting, a large proportion of staphylococcal and enterococcal disease can be prevented by intensive efforts to prevent skin breakdown and pressure ulcers, aspiration precautions, proper sterile technique in urinary or intravenous catheter insertion, discontinuation of invasive catheterization as early as possible, and sterile surgical technique. In the hospital setting, current infection control efforts regarding antibiotic-resistant staphylococcal and enterococcal disease center around contact isolation of patients either infected or colonized with MRSA and VRE and restriction of broad-spectrum antimicrobial therapy to appropriate indications. While several prior studies have shown reduction in MRSA infection with active surveillance efforts combined with rapid contact isolation of those colonized (29), the recent shift in MRSA disease into the community setting calls the efficacy of this strategy into question. More recent studies of universal surveillance for MRSA on hospital admission combined with topical decolonization have yielded

**Table 2** Risks for acquisition of staphylococcal disease in the community setting and potential interventions

Risk	Intervention
Contact (skin to skin)	Covering all infected wounds until healed
Cleanliness (lack of)	Regular bathing with soap and water Thorough and frequent hand washing Frequent fingernail trimming
Compromised skin integrity	Frequent skin moisturization Prompt recognition of small cuts and abrasions
Contaminated objects, surfaces, and items	Avoiding contact with infected persons' wound dressings Avoiding sharing of personal hygiene items and towels
Crowded living conditions	Isolation of infected individuals living in communal settings (retirement homes, long-term care facilities, shelters, etc.)

mixed results: one universal surveillance program, instituted among surgery patients at a teaching hospital in Switzerland, failed to reduce nosocomial MRSA infection (30), while another universal surveillance program, instituted broadly across a three-hospital university system, was associated with significant reduction in MRSA disease during admission and 30 days after discharge (31). Contact isolation has many downsides, as isolated patients are more likely to experience adverse events, more likely to file a formal complaint with the hospital, more likely to not have vital signs appropriately recorded, and more likely to have more days without a physician progress note (32). Thus, significant controversy exists regarding the role of universal surveillance and subsequent contact isolation for patients colonized with MRSA (33).

## **Enterococci**

### ***Introduction***

Once viewed as parts of normal flora and rarely pathogenic, enterococci have emerged as important pathogens, especially in healthcare-associated infections (34). These organisms are intrinsically resistant to many antimicrobial agents and have acquired resistance to aminoglycosides and vancomycin. They are very hardy, can colonize the gastrointestinal tract of patients, and can be spread from patient to patient in closed environments (35). Risk factors for acquisition of antibiotic-resistant enterococcal colonization and disease are similar to those associated with development of MRSA colonization and disease: underlying severity of illness, presence of invasive devices, and prior receipt of antibiotics (particularly cephalosporins) (36). Taken together, these features have enhanced the importance of this organism in geriatric patients who often have frequent or continuous contact with healthcare systems.

In addition to their increasing role in healthcare-associated infections, enterococci continue to be isolated from polymicrobial infections acquired in the community associated with the hepatobiliary system, gastrointestinal tract, or female genital tract. They also are not infrequent isolates from urinary tract infections and, occasionally, can cause endocarditis. Advanced age is a risk factor for these infections.

### ***Epidemiology and Clinical Relevance***

Enterococci are gram-positive catalase-negative cocci that classically belonged in the Lancefield classification to group D streptococci. In the 1980s, they were reclassified into their own genus. The most common and important species in human infection is *Enterococcus faecalis*, which is responsible for about 75% of infections. *Enterococcus faecium* is increasing in its frequency of isolation.

It is found in 15–20% of clinical isolates and is typically more resistant to antimicrobials, especially vancomycin (34).

Most enterococci are intrinsically resistant to many antimicrobials. They have minimum inhibitory concentrations that are very high for cephalosporins and semisynthetic penicillins, due to low affinity of their penicillin binding proteins for these agents. They appear to take up aminoglycosides poorly and thus resist usual concentrations of these agents. Trimethoprin–sulfamethoxazole often appears active in vitro but often fails in vivo; this is apparently due to the organism's ability to take up folate (37). Along with intrinsic resistance, enterococci have been remarkable in their ability to acquire antimicrobial resistance. In a sense, behaving more like gram-negative bacilli, these organisms have acquired plasmids and transposons often through conjugation mediating high-level aminoglycoside resistance, penicillinase production, erythromycin resistance, and quinolone resistance (38). The selective pressure of antimicrobial therapy in hospitals and nursing homes has favored the persistence of these resistant strains and has challenged preventive strategies.

## *Clinical Manifestations*

### **Community: Acquired Disease**

#### Urinary Tract Infection

Enterococci are rare isolates from acute uncomplicated UTI. In contrast, advancing age, male sex, and recent instrumentation are risk factors for infection due to enterococci. When possible, performing a Gram stain of urine can provide an early clue by showing gram-positive cocci in chains. When upper tract signs are present, such as fever, flank pain, leucocytosis, or chills, presumptive therapy should include an agent active for this pathogen.

#### Endocarditis/Bacteremia

Enterococci are isolated from 5 to 10% of cases of native valve endocarditis and a similar proportion of both early and late prosthetic valve endocarditis (39). Most patients with native valve endocarditis are males over 60, who give a recent history of genitourinary manipulation. Since 15–20% of males will harbor enterococci in the anterior urethra, it is assumed transient bacteremia seeds an abnormal valve.

Nosocomial endocarditis is increasingly recognized. Enterococci can colonize indwelling vascular devices; this also can be a source for seeding. These nosocomial bloodstream infections mirror the prevalent institutional strains in susceptibility to antimicrobials.

## Soft-tissue and Intraabdominal Infections

Enterococci are found in the feces of most adults and are commonly isolated from wounds or intraabdominal sites (38). These infections often improve without therapy directed specifically for this organism, and treatment focused on other components of mixed flora is often effective. When patients fail to respond or have positive blood cultures for enterococci, alternative therapy is warranted.

## Nosocomial Disease and Resistance to Antimicrobials

Broad estimates of the importance of enterococci, as nosocomial pathogens, come from the National Nosocomial Infection Surveillance system from the Centers for Disease Control and Prevention, which shows this pathogen is the third most frequent isolate and a cause of 10% of bacteremia and over 15% of UTIs in the nosocomial setting (34). Long-term care facilities also encounter issues related to enterococci; especially challenging is vancomycin-resistant enterococci (VRE). Colonization rates for VRE have ranged from 10 to 47% (41).

Conversely, knowledge of susceptibilities in the acute care facilities referring to long-term care is central to control practice and presumptive therapy selection for infections arising in long-term care. Antimicrobial resistance is a feature accounting for much of the concern over infection with enterococci. Resistance to aminoglycosides, beta-lactamases, and vancomycin, which are cornerstones of therapy for enterococcal infection, is of particular significance.

High-level resistance to gentamicin is usually plasmid mediated and a result of the production of a bifunctional fusion protein. This protein has both acetyltransferase and phosphotransferase aminoglycoside-modifying activity, conferring resistance to all aminoglycosides except streptomycin. Adding gentamicin or amikacin to a beta-lactam or vancomycin, to obtain synergy, fails in these high-level gentamicin-resistant strains. Resistance to penicillin in enterococci occurs by two mechanisms. In *E. faecalis*, strains have been isolated containing beta-lactamase. These strains hydrolyze penicillin or ampicillin, but imipenem remains active, as does vancomycin. More problematic is *E. faecium*, which resists the action of beta-lactams due to poor affinity of the penicillin binding proteins for these agents. Vancomycin is active for the usual strains. Given the reliance on vancomycin as back-up therapy for many resistant strains, the report of vancomycin resistance in 1988 was very disturbing (42). Vancomycin resistance is now widely distributed in hospitals and long-term care worldwide. Vancomycin acts by binding to the terminal D-alanine–D-alanine amino acids of the pentapeptide-containing precursor of the bacterial cell wall. The various vancomycin resistance genes, of which Van A and Van B are common, create pentapeptides ending in amino acids to which vancomycin cannot bind, for instance D-alanine–D-lactate. As a consequence, many strains now circulate, especially in hospitals, where only newly released antimicrobials such as linezolid are active.

## Treatment

Endocarditis, meningitis, and very likely bacteremia in the setting of neutropenia require bactericidal therapy. For usual strains of enterococci, this is accomplished by combining an aminoglycoside with a cell-wall agent; this is often ampicillin or vancomycin. For soft tissue and UTIs, single-agent therapy is recommended with ampicillin, which is the preferred agent. For VRE, choices are limited (see Table 1). For uncomplicated urinary tract infections, the nitrofurantoin can be used in patients with good renal function but lack tissue penetration for other sites. The usual drug selected in the treatment of VRE is linezolid (or rarely quinupristin–dalfopristin and only for *E. faecium*). Daptomycin and tigecycline have in vitro activity vs. VRE, although experience with their use in treatment of complicated VRE infections remains limited.

## Conclusions

In short, staphylococci and enterococci are responsible for a wide diversity of infections that cause significant morbidity and mortality in the aging population. While the severity of these infections has seemed to remain stable over time (with the possible exception of CA-MRSA infection, which has disproportionately affected younger populations), antibiotic resistance has increased. Thus, rapid recognition of clinical syndromes, knowledge of the local epidemiology of antibiotic resistance, and, when possible, assiduous culturing and determination of antibiotic susceptibility has become vitally important in and for the management of these infections. As the burden of disease is increasingly shifting from the inpatient to outpatient setting, prevention efforts aimed at reducing acquisition of disease in the outpatient setting are likely to be of increasing benefit.

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# Fungal Infections

Carol A. Kauffman

## Key Points

- Older adults are at increased risk of developing opportunistic fungal infections because organ transplantation, intensive cancer chemotherapy regimens, and anti-tumor necrosis factor agents are now used more commonly, and because admission to an intensive care unit, which carries many risk factors for fungal infection, has become commonplace in this group.
- *Candida* species are the most common cause of opportunistic fungal infections, and bloodstream infections are usually treated with fluconazole or an echinocandin antifungal agent.
- Invasive mold infections are mostly caused by *Aspergillus* species; in older adults, they cause primarily pulmonary and sinus infections, and they are associated with a high mortality rate.
- The endemic fungi, *Histoplasma capsulatum*, *Coccidioides* species, and *Blastomyces dermatitidis*, cause infection when the mold form is dispersed and inhaled from the environment in those specific areas of the country in which these organisms flourish.
- Amphotericin B is used for initial treatment of severe histoplasmosis, coccidioidomycosis, and blastomycosis; itraconazole is the therapy of choice for most mild to moderate infections due to these endemic mycoses.

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## Introduction

Serious fungal infections can be separated into two major categories: The opportunistic mycoses that include candidiasis, cryptococcosis, and invasive mold infections such as aspergillosis and zygomycosis, and the endemic mycoses, which in the United States, includes histoplasmosis, blastomycosis, and coccidioidomycosis. The fungal infections represented in these broad categories differ with respect to the characteristics of the organisms causing infection, their epidemiology, the clinical manifestations, the approach to diagnosis, and the principles guiding therapy.

In response to these different groups of fungi, host defense mechanisms also differ. Except in immunocompromised hosts, serious infection with the opportunistic mycoses is rare. In contrast, the endemic mycoses are true pathogens that cause disease in both healthy and compromised hosts. However, the severity of infection with the endemic mycoses is determined in part by the host's response.

## Opportunistic Fungal Infections

### *Epidemiology and Clinical Relevance*

As the number of immunocompromised patients has risen, opportunistic fungal infections have increased dramatically in recent years. In the last decade, the elderly appear to be at increasing risk for infections with the opportunistic fungi. There are several reasons for this enhanced risk. First, with increasing realization that older adults with cancer should not be excluded because of age from intensive chemotherapeutic treatment regimens, there are more immunosuppressed older cancer patients. Second, as evidence for the efficacy and safety of transplantation in this population has accrued, solid organ transplantation is now more common in patients over the age of 60. Third, immunosuppressive regimens, including the use of anti-tumor necrosis factor agents, are now routine in the management of rheumatologic and dermatologic conditions often found in older adults. Fourth, and possibly the most important risk factor for older adults, is the increasing role of treatment in intensive care units with the use of life-support systems, catheters, and broad-spectrum antibiotics.

### **Candidiasis**

The increase in opportunistic infections in elderly patients is primarily due to an increase in infections with *Candida* species. The spectrum of disease varies from localized infections such as oropharyngeal candidiasis to candidemia and disseminated candidiasis.

Factors that predispose older patients to the development of oropharyngeal candidiasis include xerostomia, broad-spectrum antibiotics, inhaled corticosteroids,

and dentures (1). Age alone does not appear to be an independent risk factor for the development of oropharyngeal candidiasis. In older adults, the presence of systemic diseases and a multiplicity of medications frequently lead to xerostomia, which then enhances *Candida* colonization of the mucosa. Denture stomatitis due to *Candida* species is very common (see also chapter “Orofacial and Odontogenic Infections in the Elderly”). Patients who do not remove their dentures at night, and those who have poor oral hygiene, are more likely to have this manifestation of candidiasis.

In contrast to other *Candida* infections, *Candida* vulvovaginitis is unusual in older women (2). Without estrogen stimulation, the vaginal epithelium becomes thin and atrophic, glycogen production decreases, vaginal pH rises, and colonization by *Candida* decreases.

Candiduria is seen more often in older adults than in younger persons (3). The risk factors for candiduria include diabetes mellitus, obstructive uropathy, neurogenic bladder, indwelling urinary catheters, prior surgical procedures, intensive care stay, and antibiotic therapy (3). In older adults, many of these factors occur with increasing frequency.

*Candida* species are the fourth most common cause of nosocomial bloodstream infections. Several studies have found that those over 60 constitute the majority of patients with candidemia and also have the highest mortality rates (4). Elderly patients at the highest risk are those in an intensive care unit who are on broad-spectrum antibiotics, have an indwelling central venous catheter in place, are receiving parental nutrition, require renal replacement therapy, and have had a surgical procedure. *C. albicans* is the species most commonly found to cause candidemia, but other species, especially *C. glabrata*, are an increasing problem. Several studies have found that *C. glabrata* occurs disproportionately in older adults (5, 6) but the reasons for this have not been elucidated.

## Cryptococcosis

In older persons, cryptococcosis is increased modestly. Approximately 25% of cases of cryptococcal meningitis not associated with human immunodeficiency virus (HIV) infection are in persons over age 60. The underlying conditions most often noted are hematologic malignancy, organ transplantation, corticosteroids, and cirrhosis. However, 25–30% of patients have no overt underlying immunosuppressive condition, and many of these patients are older adults. In older patients who have cryptococcal meningitis, mortality appears to be increased (7).

## Mold Infections

Although many different types of molds have been described as occasional pathogens in immunosuppressed patients, only aspergillosis and zygomycosis will be discussed. There are hundreds of *Aspergillus* species that are ubiquitous in

the environment, but very few cause infection in humans. The most common pathogenic species are *A. fumigatus* and *A. flavus*. Infection ensues when conidia (spores) are inhaled into the respiratory tract of a susceptible host. Nosocomial *Aspergillus* infections are often traced to hospital construction. Depending almost entirely on the immune response of the host, a wide spectrum of infections can occur. Although less common than candidiasis, *Aspergillus* infections are life threatening in immunosuppressed patients. Several forms of aspergillosis, specifically chronic necrotizing pulmonary aspergillosis and sino-orbital aspergillosis, appear to occur more often in older adults (8, 9).

Zygomycosis, also known as mucormycosis, is an uncommon, but often, lethal infection; there is no age predilection. The major genera identified are *Rhizopus* and *Mucor*. The risk factors for zygomycosis include diabetes, hematologic malignancies with neutropenia, organ transplantation, and deferoxamine chelation therapy for iron overload (10). Because of the increased risk of myelodysplastic syndrome and subsequent need for repeated transfusions with increasing age, the latter circumstance is likely the only one in which older adults may be over-represented.

## ***Clinical Manifestations***

### **Candidiasis**

White plaques on the buccal, palatal, or oropharyngeal mucosa that can easily be removed are typical of oropharyngeal candidiasis. Angular cheilitis and diffuse erythema, which is often present beneath upper dentures, are also manifestations of oropharyngeal candidiasis. Because typical plaques are absent, the diagnosis may be overlooked (1).

*Candida* vaginitis usually presents with pruritus and vaginal discharge that may range from “cottage cheese-like” to thin and watery (2). When cheesy material is absent, *Candida* vulvovaginitis must be differentiated from atrophic vaginitis.

Most patients with candiduria are asymptomatic and are merely colonized (3). Fewer than 5% of patients have dysuria and frequency, and even fewer have symptoms of upper tract infection. Rarely, obstructive symptoms and renal failure have been noted secondary to fungus balls composed of masses of fungi.

The manifestations of systemic infection with *Candida* species are quite varied (see Table 1). After entering the bloodstream, either from an intravenous catheter or the gastrointestinal (GI) tract), the organism disseminates widely, causing microabscesses in many organs, including eye, kidney, liver, spleen, myocardium, and brain. Patients with candidemia have symptoms that are indistinguishable from those associated with bacteremia (6, 11). Some are quite ill with a sepsis picture, but others may have only unexplained fever. Skin lesions occurring during the course of candidemia appear as tiny pustular lesions on an erythematous base and provide a clue to the presence of candidemia (see Fig. 1).

**Table 1** Systemic opportunistic fungal infections in older adults

Fungal infection	Risk factors	Usual clinical manifestations
Candidiasis	Neutropenia, hematologic malignancy, corticosteroids, transplant, ICU, antibiotics, IV catheters, parenteral nutrition, GI surgical procedure	Fever, pustular skin rash, hypotension; may have specific organ involvement
Cryptococcosis	Hematologic malignancy, transplant, cirrhosis, corticosteroids; ~25% have no risk factor identified	Headache, fever, cranial nerve palsy, confusion; cough, dyspnea, sputum production for pulmonary infection
Aspergillosis	Neutropenia, hematologic malignancy, corticosteroids, transplant	Fever, pleuritic chest pain, cough; eye/sinus pain, proptosis, ophthalmoplegia, visual loss
Zygomycosis	Diabetes mellitus, hematologic malignancy, neutropenia, transplant, deferoxamine chelation therapy	Eye/sinus pain, necrotic eschar (palate, nares) cavernous sinus thrombosis; fever, pleuritic chest pain, cough

ICU intensive care unit, IV intravenous, GI gastrointestinal



**Fig. 1** Typical skin lesions seen in patients with disseminated candidiasis

## Cryptococcosis

Although the major manifestation of infection with *C. neoformans* is meningitis, the pathogenesis of infection begins with inhalation of the organism from the environment and subsequent pulmonary infection. The chest radiograph may show nodular infiltrates, a pleural-based mass, cavitary lesions, or diffuse infiltrates (12) (see Fig. 2). However, most often, the pulmonary infection is asymptomatic, and clinical manifestations of cryptococcosis occur only after the organism has spread to the central nervous system. Elderly patients may not have the usual symptoms of fever, headache, and cranial nerve palsies but instead can present solely with confusion without fever, nuchal rigidity, or focal neurologic findings (see Table 1).

## Mold Infections

*Aspergillus* invasion of the upper respiratory tract leads to sinusitis and may proceed to invasion of the orbit. In patients with neutropenia, the acute onset of pain, erythema, fever, serosanguinous drainage, and proptosis is seen. In older patients



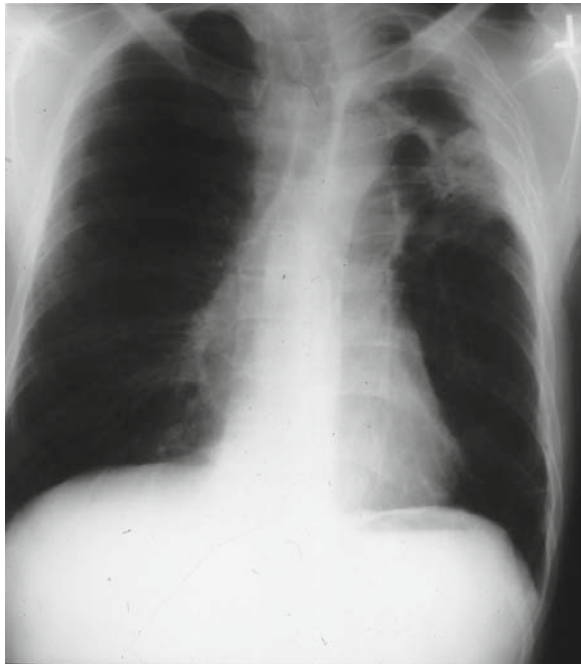
**Fig. 2** Right lower lobe infiltrate due to cryptococcosis in a 67-year-old man who was on corticosteroids and who had confusion, headache, and fever. Sputum and cerebrospinal fluid yielded *C. neoformans*



who are not immunosuppressed, but who may have been on corticosteroids or are diabetic, *Aspergillus* causes a subacute sino-orbital infection with pain, proptosis, ophthalmoplegia, and loss of vision due to invasion of the apex of the orbit (8). Most patients are thought to have a retro-orbital tumor until biopsy reveals hyphae and inflammatory debris.

Acute pulmonary aspergillosis in immunosuppressed patients presents with fever, pleuritic chest pain, and dyspnea and has a rapidly progressive downhill course if not treated promptly (see Table 1). Chronic necrotizing pulmonary aspergillosis, occurring mostly in middle-aged to elderly men with chronic obstructive pulmonary disease, is a subacute illness. Low-dose corticosteroids and broad-spectrum antibiotics are predisposing factors for this form of aspergillosis. Patients have fever, cough, purulent sputum, weight loss, and pleuritic chest pain. Multilobar involvement is common, cavity formation is the rule, and extension to the pleura is frequent (see Fig. 3). Progressive pneumonia is the rule unless the diagnosis is made and appropriate therapy given.

Patients with zygomycosis are usually quite ill. Diabetics most often have the rhinocerebral form (10) (see also chapter “Infections in Diabetics”). A black eschar can be seen on the palate or around the orbit, and serosanguinous material is found on endoscopic examination of the sinuses (see Table 1). Orbital invasion progresses rapidly to cavernous sinus thrombosis and can culminate with cerebral infarction. In patients with pulmonary zygomycosis, the chest radiograph shows wedge-shaped



**Fig. 3** Chronic necrotizing pulmonary aspergillosis in a middle-aged man with no known risk factors other than chronic obstructive pulmonary disease



**Fig. 4** Right upper lobe zygomycosis in an elderly man who had myelodysplasia leading to dependence on transfusions and treatment with deferoxamine chelation

or nodular infiltrates, which cavitate as necrosis progresses (see Fig. 4). Localized cutaneous forms occur and generally carry a better prognosis than rhinocerebral or pulmonary zygomycosis.

### ***Diagnostic Tests***

Because of the life-threatening nature of these infections, the diagnosis of a systemic opportunistic fungal infection must be made promptly. Growth in culture of opportunistic fungi is rarely difficult; cultures are usually positive within a few days. The major complicating issue is that organisms as ubiquitous in the environment as *Aspergillus* or *Rhizopus* can easily contaminate specimens. Therefore, growth in culture must be carefully assessed as to whether it truly reflects infection (13). Confounding the diagnosis of candidiasis is the fact that *Candida* are normal flora in the GI and genitourinary (GU) tracts and on skin, and thus, growth from samples taken from non-sterile body sites often means only colonization. However, growth of *Candida* from blood or normally sterile body fluids is obviously significant. In contrast to the other opportunists, *C. neoformans* is neither common in the environment nor part of the normal flora, and thus growth of this organism in culture always reflects infection.

Especially in immunocompromised patients who are acutely ill, histopathologic demonstration of fungi in tissues is a very important diagnostic tool. Unfortunately,

the invasive procedures necessary to obtain lung or other tissue are often precluded in extremely ill immunosuppressed patients. For cryptococcosis, examination of cerebrospinal fluid (CSF) with an India ink preparation that highlights the large capsule of *C. neoformans* is a quick and reliable test.

Antibody tests have not proved to be useful for the diagnosis of opportunistic fungal infections. Detection of fungal cell wall antigens is preferred. The latex agglutination test for cryptococcal polysaccharide antigen has excellent sensitivity and specificity and is routinely performed in both serum and CSF (14). The galactomannan enzyme immunoassay detects an *Aspergillus*-specific cell wall antigen and has proven most useful in the highest risk patients, such as stem cell transplant recipients (15). The galactomannan assay has not been studied in patients with chronic necrotizing pulmonary aspergillosis, and it is likely that it will not be useful for sino-orbital aspergillosis. Other non-culture-based systems for invasive mold infections have not proved useful thus far.

## ***Treatment***

### **Candidiasis**

Treatment of oropharyngeal candidiasis with a topical agent, such as clotrimazole troches, is appropriate first-line therapy. Fluconazole, 100 mg daily, should be reserved for patients with severe disease or denture stomatitis that is often difficult to treat (1).

Vaginal candidiasis is easily treated with topical antifungal agents such as miconazole or clotrimazole creams. However, fluconazole, 150 mg orally as a single dose, is an attractive alternative, especially for those patients who have underlying illnesses that make topical therapy difficult to use (2, 16).

Candiduria often disappears with removal of the predisposing factors, especially indwelling urethral catheters and antimicrobial agents (3). When candiduria is persistent and shown to be causing symptoms, the most appropriate treatment is fluconazole, 200 mg daily for 14 days (16, 17). The use of amphotericin B bladder irrigation is discouraged.

Amphotericin B, previously the mainstay of treatment for serious *Candida* infections, is now rarely used this indication. Currently, candidemia is treated most often with fluconazole, 400 mg/day after an initial 800 mg loading dose, or with an echinocandin (16). Three echinocandin agents are available, caspofungin, micafungin, and anidulafungin, and all three appear to have equivalent efficacy for candidemia (16). The echinocandins are extremely safe, and they have activity against those species of *Candida*, especially *C. glabrata*, that are often resistant to fluconazole (18). All intravascular lines should be removed or replaced, and treatment should be continued for 2 weeks beyond the time that blood cultures no longer yield *Candida* unless a focal infection is discovered that will require longer therapy.

## **Cryptococcosis**

The most appropriate therapy for cryptococcal meningitis in older adults has not been specifically studied, but trials in acquired immunodeficiency syndrome (AIDS) patients with cryptococcal meningitis have shown that the best results are obtained when induction therapy is carried out with the combination of amphotericin B (0.7 mg/kg/day) and flucytosine (100 mg/kg/day) for at least 2 weeks, followed by consolidation therapy with fluconazole, 400 mg/day for a minimum of 10 weeks (19). Initial therapy with fluconazole alone is not adequate for patients with meningitis but has been effective for patients with isolated pulmonary cryptococcal infection (20). In spite of appropriate therapy for meningitis, symptoms of dementia may not improve in older patients.

## **Mold Infections**

The antifungal agent of choice for treating all forms of aspergillosis is voriconazole, an extended-spectrum azole that has been shown to be superior to amphotericin B for invasive aspergillosis (21). This agent, which can be given either intravenously or orally, has many drug–drug interactions and is best given with the help of a clinical pharmacist or infectious diseases consultant. The echinocandins also have activity against *Aspergillus* species, but are considered second-line therapy, available if the patient cannot tolerate voriconazole (18). Finally, amphotericin B, previously the agent of choice, can also be used for invasive aspergillosis, but toxicity is much greater than that of the azoles or the echinocandins, and it cannot be recommended for older adults.

The treatment of zygomycosis involves correction of the underlying immune defect, aggressive debridement of all necrotic tissue, and antifungal treatment with a lipid formulation of amphotericin B, 5–10 mg/kg daily (22). A new azole agent, posaconazole, has been used as salvage therapy in patients who initially had been treated with amphotericin B and offers a new option for step-down oral therapy for this devastating infection (23).

## **Endemic Mycoses**

### ***Epidemiology and Clinical Relevance***

As the population of the United States ages, and as older adults remain in better health for a longer period of time, they travel more extensively, visit more exotic places, and experience different outdoor activities such as those arranged on eco-tours that increase their exposure to endemic mycoses. These fungi are found in soil or vegetation; each has its own ecological niche from which it is aerosolized and subsequently inhaled (see Table 2). Older persons may become infected while traveling

**Table 2** Endemic mycoses in older adults

Fungal infection	Geographic distribution	Common clinical syndromes
Histoplasmosis	Ohio and Mississippi river valleys	Acute pneumonia, chronic cavitary pulmonary infection, chronic progressive disseminated infection
Blastomycosis	Southeastern, south central, and north central states; Ontario and Manitoba	Pneumonia, mass-like or cavitary pulmonary lesions, verrucous skin lesions, prostatitis
Coccidioidomycosis	Arizona, southern California, New Mexico, western Texas	Acute pneumonia, cavitary pulmonary lesions, ulcerated skin lesions, lytic bone lesions, meningitis

in an area endemic for a certain fungus, but symptoms often appear only after they return home. Older adults who spend the winter months in the desert southwest may develop symptoms of coccidioidomycosis only after returning home. A patient who consults a physician in Minnesota with symptoms related to coccidioidomycosis that was acquired in southern California may be the first patient with this infection ever seen by the Minnesota physician, and the correct diagnosis may not be made.

Several endemic mycoses have the propensity to reactivate as immunity wanes with increasing age or because of immunosuppressive medications or diseases. This reactivation event might occur in a person who retired to an area of the country outside of the endemic area for a particular fungal infection. Thus, although physicians in the southwestern United States are very familiar with coccidioidomycosis, histoplasmosis or blastomycosis might be overlooked in a patient from Kentucky who has retired to Arizona and only then develops signs of an endemic mycosis acquired years before in Kentucky.

The increasing use of the anti-tumor necrosis factor agents, etanercept (Enbrel), infliximab (Remicade), and adalimumab (Humira), for rheumatoid arthritis, inflammatory bowel disease, and several dermatological conditions in older adults has increased the risk for development of histoplasmosis and coccidioidomycosis (24, 25). These mycoses require cell-mediated immunity to eradicate the organism, and severe disseminated infections have occurred in patients who have either become newly infected or have experienced reactivation of a prior focus of infection.

HIV infection is an increasingly reported problem in the older population and constitutes another risk factor for development of either newly acquired or reactivation infection with *H. capsulatum* or *Coccidioides* species (see also chapter “Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome”). Not only is the risk higher for development of these infections, but the severity of the infection is also increased.

## Histoplasmosis

*H. capsulatum* is endemic in the Mississippi and Ohio River valleys and throughout much of Central America. It is estimated that hundreds of thousands of people are infected each year, but usually the illness is self-limited with minimal flu-like symptoms.

However, severe life-threatening pneumonia and disseminated infection also occur. Histoplasmosis is the only endemic mycosis in which certain manifestations are age-specific; chronic cavitary pulmonary infection and chronic progressive disseminated histoplasmosis occur predominantly in older individuals (26).

### **Blastomycosis**

*B. dermatitidis*, the causative agent of blastomycosis, is found most frequently in the southeastern, south central, north central United States, and the Canadian provinces of Ontario and Manitoba. Outbreaks have occurred in groups involved in outdoor activities, but most cases are sporadic and a specific point source of infection cannot be found. For blastomycosis, there is no evidence that older individuals are at more risk for developing infection than younger persons, but the mortality does appear to be greater in those age 65 years and older (27).

### **Coccidioidomycosis**

As the exodus of retirees to the southwestern United States continues, first-time exposure to *Coccidioides* species has increased in older adults. This organism proliferates in the deserts of Arizona and California that are typified by flora such as the saguaro cactus. There are now known to be two species of *Coccidioides*, *C. immitis* in southern California, and *C. posadasii* in the other areas of the southwestern United States, Central America, and South America. The conidia are widely dispersed during windstorms and are highly contagious.

Several recent epidemics of coccidioidomycosis have occurred in Arizona and southern California, and thousands more individuals have been infected (28). Two important trends have been noted recently. There has been a shift in the age of patients with symptomatic coccidioidomycosis so that the annual incidence rate for coccidioidomycosis is now highest in those age 65 years and older (29). Also, older individuals and those with diabetes are more likely to develop severe pulmonary coccidioidomycosis (30). For reasons that have never been clarified, dark-skinned races, especially African American and Filipino, are more likely to experience disseminated infection than white-skinned races.

### ***Clinical Manifestations***

The pathogenesis of the endemic mycoses is similar in that infection starts almost always with inhalation of conidia from the mold phase of the organism in the environment. Thus, pulmonary manifestations are prominent in many patients. These fungi have the propensity to silently disseminate through the bloodstream to many different organs and then cause a variety of different manifestations either at the time of the initial infection or months to years later.

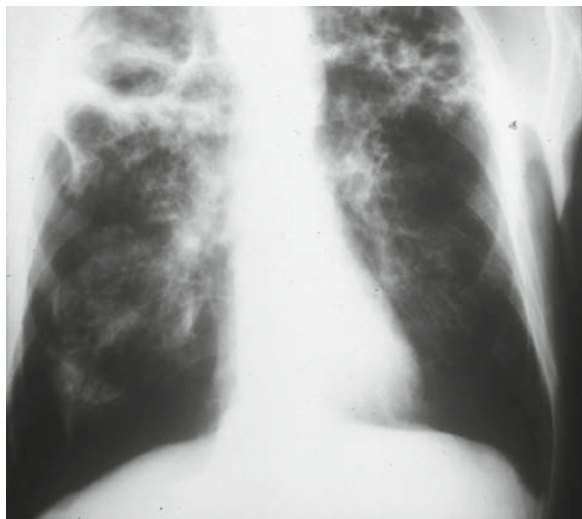
## Histoplasmosis

Two forms of histoplasmosis are seen most often in older adults (see Table 2). Chronic cavitary pulmonary histoplasmosis affects mostly middle-aged and elderly men who have emphysema (31). Patients with this form of histoplasmosis have constitutional symptoms of fatigue, weakness, fever, night sweats, and weight loss. Pulmonary symptoms include dyspnea, cough, sputum production, and hemoptysis. The disease is subacute to chronic in its course. Upper lobe cavitary disease with extensive lower lobe fibrosis is the usual chest radiographic finding (see Fig. 5). Progressive pulmonary insufficiency and death occur unless treatment is given.

Another form of histoplasmosis that occurs mostly in middle-aged to elderly men is progressive disseminated disease (31). In this form of histoplasmosis, the host is unable to eradicate the organism from parasitized macrophages, and the disease is fatal if untreated. The clinical manifestations of progressive disseminated histoplasmosis include fever, fatigue, anorexia, and weight loss. Dyspnea and cough are often present, lesions on the buccal mucosa, tongue, palate, or oropharynx are common, and hepatosplenomegaly is usual. Because of adrenal infiltration and destruction, the patient may also present with symptoms of Addison's disease. Pancytopenia and increased alkaline phosphatase are frequent, and diffuse pulmonary infiltrates are often present on chest radiograph.

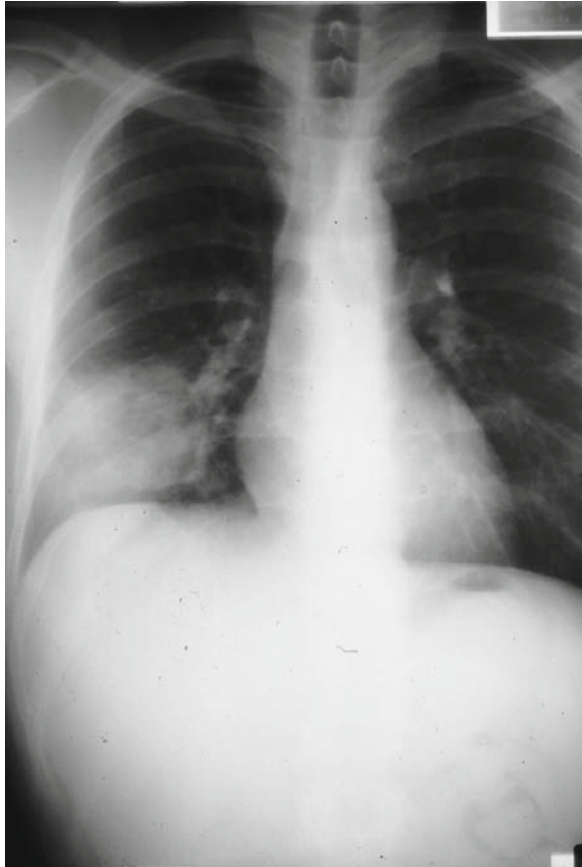
## Blastomycosis

In older patients, pulmonary blastomycosis can mimic tuberculosis with dyspnea, cough, sputum production, fever, weight loss, and fatigue (see Table 2). The pulmonary lesions can be mass-like and mistaken for lung cancer, cavitary, or nodular in



**Fig. 5** Chronic cavitary pulmonary histoplasmosis in an elderly man with severe emphysema

**Fig. 6** Pulmonary blastomycosis initially thought to be lung cancer. Bronchoscopy with biopsy showed granulomas and thick-walled budding yeasts typical of *B. dermatitidis*



appearance (32) (see Fig. 6). Rarely, patients develop acute overwhelming pneumonia and acute respiratory distress syndrome (ARDS) (33).

Although blastomycosis begins in the lungs, subsequent dissemination to other organs is common. Frequently, the only clinical symptom is the development of one or multiple skin lesions that are usually slowly enlarging, verrucous, and have discrete punctate areas of purulence (see Fig. 7). Osteoarticular structures are frequently involved, as is the GU tract, in which the most frequently targeted organ is the prostate.

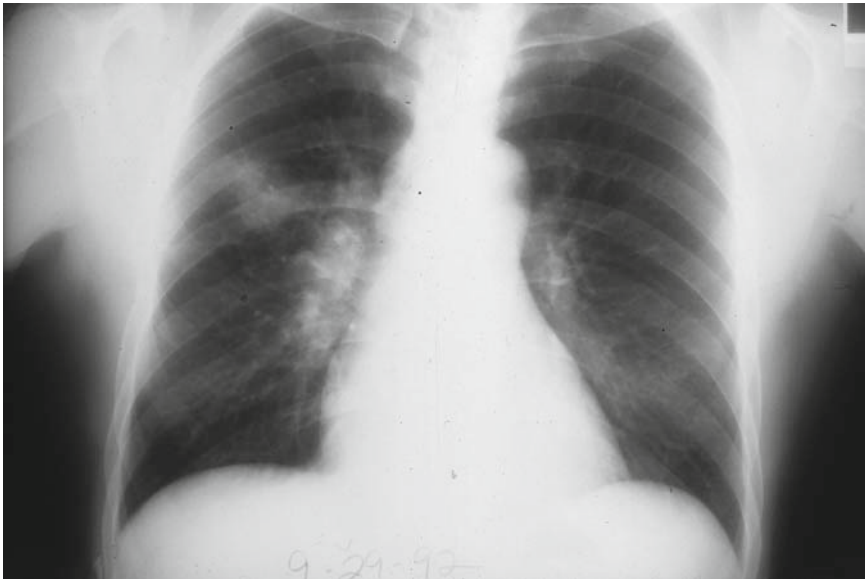
### **Coccidioidomycosis**

Coccidioidomycosis presents in many different ways (see Table 2). Patients experiencing primary disease usually have a self-limited flu-like illness consisting of fever, cough, headache, and fatigue. Patchy pneumonitis is seen on chest radiograph





**Fig. 7** Typical indolent verrucous skin lesions of blastomycosis on the hands and legs of an elderly gentleman (photo courtesy of Dr. Gunner Deery)



**Fig. 8** Right upper lobe pneumonia due to *Coccidioides* species in a 52 year-old African American marine sent to southern California

(see Fig. 8). Complications include the development of persistent thin-walled cavities and less commonly, chronic pulmonary disease (34). The latter occurs predominantly in patients with underlying emphysema and/or diabetes mellitus (30). Diffuse pulmonary infiltrates have been noted primarily in patients who have disseminated infection and are more common in those who are immunosuppressed (35).

The organs most frequently involved with disseminated coccidioidomycosis are skin, bone, and meninges. Meningitis, the most feared complication, presents with chronic headache months after the initial infection and can be especially difficult to diagnose in an elderly patient returning from the southwest to other areas of the country. The course of coccidioidal meningitis is protracted, and a successful outcome is not assured, especially in older adults.

### *Diagnostic Methods*

The approach to diagnosis is similar for all of the endemic mycoses. Cultures obtained from the infected tissue; histopathologic or cytologic examination of tissue, body fluids, or purulent material; antibody tests; and antigen detection are variably useful for each infection.

The most definitive method of diagnosis is growth of the organism, but for histoplasmosis and blastomycosis growth may take 4–6 weeks. *Coccidioides* species usually grow on fungal or regular media within several days. *Coccidioides* is highly contagious and is classified as a bioterrorism agent. In the laboratory setting, it must be handled under a hood using biosafety level 3 precautions. Clinicians must inform the laboratory that coccidioidomycosis is a possibility to avoid transmission to technicians.

Histopathologic or cytologic demonstration of the organism in tissues or body fluids is extremely helpful for diagnosis, especially for those patients who are acutely ill. The typical thick-walled yeasts of *B. dermatitidis*, showing single broad-based buds are readily identified in cytological or calcofluor white preparations of sputum and tissue biopsies. The tiny intracellular yeast forms of *H. capsulatum* are best visualized in tissues using methenamine silver stains. *Coccidioides* species are quite distinctive in tissues; the large spherules (80–100  $\mu\text{m}$ ) are readily identified in tissue and also in purulent drainage.

Serology plays an important role in the diagnosis of histoplasmosis and coccidioidomycosis (31, 36). A positive test prompts the clinician to consider more invasive procedures such as bronchoscopy, bone marrow aspiration, or liver biopsy in order to establish a diagnosis. There are occasions when the only evidence for infection is the presence of antibodies; this is especially true of meningitis, in which both fungi are exceedingly difficult to grow but CSF serology is positive. For blastomycosis, specific and sensitive antibody assays are not available.

An enzyme immunoassay that detects a cell wall antigen of *H. capsulatum* has proved to be extremely useful for the diagnosis of disseminated histoplasmosis (37). The sensitivity is approximately 90% in patients who have a large burden of organisms; this includes patients who have AIDS and those who are immunosuppressed. It is not specific, however, showing cross-reactivity with blastomycosis and coccidioidomycosis. A similar assay has been developed for *B. dermatitidis*. It is too early to know how useful this development will be, but it is known that false positives occur in patients with histoplasmosis (38).

## *Treatment*

Treatment of the endemic mycoses is similar in regard to the antifungal agents that are used. For severe infections with any of the endemic mycoses and for those who have central nervous system involvement, amphotericin B is the agent of choice. Increasingly lipid formulations of amphotericin B are used, especially in older adults who often have reduced renal function. The lipid formulations are less toxic than standard amphotericin B, but are not free of toxicity, usually require hospitalization to administer, and can be associated with severe infusion reactions. Most patients will require amphotericin B therapy until they have shown clinical improvement and then step-down therapy to an azole is recommended (39, 40).

The azole antifungal agents have revolutionized the treatment of the endemic mycoses; they are much less toxic than amphotericin B, and oral administration is a benefit when treating chronic infections. Ketoconazole was the first oral azole agent, but because of its toxicity and lesser efficacy, it has been supplanted by itraconazole. Itraconazole is the drug of choice for histoplasmosis and blastomycosis of mild to moderate severity and for step-down therapy following amphotericin B. For coccidioidomycosis, either fluconazole or itraconazole appear to be equally efficacious (41). The usual dosage of itraconazole is 200 mg twice daily (after a loading dose of 200 mg 3 times daily for 3 days), and the dosage for fluconazole is 400 mg daily (after a single loading dose of 800 mg). Therapy generally is given for 6–12 months and sometimes longer. For those patients who have coccidioidal meningitis, fluconazole is the preferred agent because of its superior CSF penetration. The dosage is 800 mg daily, and therapy must be given for life as the organism is rarely eradicated from the central nervous system (34).

Absorption of itraconazole capsules is dependent on gastric acidity and the presence of food in the stomach. Because older adults are more likely to be achlorhydric, absorption may be decreased. Histamine (H<sub>2</sub>) receptor antagonists, proton pump inhibitors, and antacids should not be used when itraconazole capsules are prescribed. However, itraconazole oral suspension does not require food or acid for absorption and is preferred for this reason. Fluconazole requires neither gastric acidity nor food for absorption.

Drug interactions, many of which have serious implications for older adults, are frequently encountered with the azole antifungal drugs (42). Interactions with warfarin, phenytoin, and carbamazepine occur in varying degrees with all of the azole drugs in current use. Itraconazole can increase serum digoxin levels with subsequent toxicity, and fluconazole can increase the effect of oral hypoglycemics. If possible, the azoles should be avoided in patients with QT prolongation on electrocardiogram and those on other medications that prolong the QT interval. In a small percentage of mostly elderly patients, itraconazole has caused the triad of edema, hypokalemia, and hypertension. All of the azole agents have been noted to cause hepatitis, and liver enzymes tests should be followed in patients taking azole agents.

In spite of these issues, the azoles are exceedingly useful in older adults with endemic mycoses. Most therapy is now given in the outpatient setting, and results for most patients with infection with an endemic mycosis are excellent.

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# Viral Infections

Coley B. Duncan and Ann R. Falsey

## Key Points

- Although influenza remains indisputably the most significant viral pathogen in adults, other viruses such as respiratory syncytial virus, parainfluenza viruses, and human metapneumovirus are now recognized as significant pathogens in older populations.
- Oseltamivir and zanamivir are antiviral agents that are effective for the treatment and prophylaxis of influenza A and B. For treatment and for optimal effect, therapy should be initiated within 48 h of symptom onset.
- Infection with hepatitis viruses may be more severe in older adults with more fulminate disease as observed with acute hepatitis A and a more rapid progression to cirrhosis with hepatitis C.
- Outbreaks of viral gastroenteritis are common in long-term care facilities, and infection may lead to death due to dehydration and oliguria.
- The incidence of herpes zoster increases with advancing age and carries with it a significant risk of post herpetic neuralgia. The use of antiviral medications and corticosteroids may reduce the incidence and severity of chronic pain.

## Respiratory Viruses

Acute respiratory tract infections (ARI) occur commonly throughout life, accounting for substantial morbidity and mortality in older adults (1). Due to influenza's epidemic nature and its ready growth in cell culture, it was commonly the only viral pathogen identified in many early etiologic studies of ARI in adults. Recent studies employing reverse transcription polymerase chain reaction (RT-PCR) and sensitive serology indicate that a wide variety of viruses including respiratory syncytial virus (RSV),

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parainfluenza viruses (PIV), human metapneumoviruses (hMPV), coronaviruses (Co-V), and rhinoviruses may cause severe disease in adults and result in hospitalization (2).

### ***Influenza (See Also Chapter “Vaccinations”)***

Together pneumonia and influenza comprise the fifth leading causes of death in persons aged 65 years and older. Influenza viruses are enveloped ribonucleic acid (RNA) viruses that are classified as A, B, or C, based on stable internal proteins (3). The virus contains two major surface proteins: hemagglutinin (H) and neuraminidase (N), which can undergo minor antigenic changes leading to yearly epidemics or major changes resulting in influenza pandemics. Currently, there are two circulating influenza A viruses, H1N1 and H3N2, in addition to influenza B, present in the United States. H1N1 viruses do not appear to cause serious problems in older persons, possibly due to previous immunity. In 1997, influenza A (H5N1), which was previously seen only in birds, crossed the species barrier and human infection occurred in Southeast Asia (4). This highly pathogenic avian influenza has spread in bird populations throughout Asia and into Europe. To date, human infection has been rare and transmission has occurred primarily by direct contact with infected birds. Unlike seasonal influenza, illness due to avian influenza is more severe in young children as compared to older adults.

### **Epidemiology and Clinical Relevance**

In a community, peak influenza activity typically lasts 6–8 weeks, with attack rates highest in preschool and school-aged children and lowest in older persons (3). Despite lower attack rates, mortality from influenza rises dramatically with age and the presence of underlying medical conditions. The presence of one high-risk medical condition (cardiovascular, pulmonary, renal, metabolic, neurologic, or malignant disease) increases the risk of death from influenza 39-fold. Despite increasing vaccine coverage, current Centers for Disease Control and Prevention (CDC) data indicate increasing influenza-related morbidity and mortality over the past decade (5). In the United States, approximately 226,000 hospitalizations and 34,000 deaths occur each year in persons age 65 years and older (6, 7). The devastating impact of influenza is most dramatically seen in long-term care facilities (LTCFs) where explosive epidemics may occur. During outbreaks, rates of pneumonia and hospitalization are as high as 52% and 29%, respectively, with case fatality rates of 30%.

### **Clinical Manifestations**

The classic presentation of influenza is an abrupt onset of fever, chills, headache, and myalgias (see Table 1). Dry cough, sore throat, and ocular pain are also common (3). Fever remains a common finding in the elderly, although the height of the fever may be lower compared with young persons. Although many elderly adults have classic symptoms, a substantial number may have more nonspecific presentations such as



**Table 1** Respiratory viral infections

	Peak season	Incubation (d)	Clinical clues	Antiviral therapies
Influenza A H1N1	Winter	1–3	High fever, headache, myalgias	Zanamivir two 5mg inhalations BID x 5 days or rimantadine 100mg po BID x 5 days*
Influenza A H3N2	Winter	1–3	High fever, headache, myalgias	Oseltamivir 75mg po BID x 5 days** or zanamivir two 5mg inhalations BID x 5 days
Influenza B	Winter	1–3	High fever, headache, myalgias	Oseltamivir 75mg po BID x 5 days** or zanamivir two 5mg inhalations BID x 5 days
RSV	Winter	3–5	Rhinorrhea, wheezing	RibavirinA***
Parainfluenza	Fall-spring	1–2	Pharyngitis, hoarseness	None
Rhinovirus	All	1–2	Rhinorrhea	None
Coronavirus	Winter-spring	1–2	Non-specific	None

RSV, respiratory syncytial virus.

\*100 mg daily for severe hepatic dysfunction, renal failure (CrCl 10 mL/min) and for elderly nursing home patients.

\*\*Dosage should be reduced in persons with creatinine clearance of < 30 mL/min

\*\*\*Ribavirin is not FDA approved for use in adults.

BID twice a day; po orally

fever and confusion or worsening of chronic medical conditions. In contrast to young healthy persons, the triad of fever, cough, and acute onset of symptoms has a positive predictive value of only 30% in elderly adults. Given the protean manifestations of influenza in older persons, it is always important to consider influenza in the differential when evaluating an acutely ill elderly adult during the winter.

Influenza lower respiratory tract involvement increases steadily with advancing age with the rates of pneumonia 4–8% in persons aged 5–50 years and rising to 73% in persons over age 70 (8). Secondary bacterial pneumonia following acute influenza also occurs more frequently in older persons. Although the rates of pneumonia rise with age, hospitalization most frequently results from exacerbation of chronic medical conditions. In addition to the immediate complications of influenza, residents of nursing homes who survive influenza experience a significant functional decline in activities of daily living.

## Diagnostic Tests

Although many physicians use clinical features to make a diagnosis of “the flu,” laboratory confirmation is best, especially if therapeutic decisions are needed because influenza may be difficult to distinguish from other respiratory viruses.

Older persons typically shed the virus for 3–5 days, although shedding up to 14 days has been documented in hospitalized patients (9). Rapid antigen testing may be done directly on nasopharyngeal specimens using an enzyme immunoassay (EIA) (10). Although not as sensitive as viral culture, rapid tests offers quick turnaround times and may be useful for infection control and treatment decisions. Sensitivity of rapid testing in adults is estimated to be 50–60% for influenza A strains and 10–20% for influenza B (11). When available, RT-PCR offers rapidity while retaining excellent sensitivity.

## Treatment

As of this writing, zanamivir or rimantadine can be used for the treatment or prophylaxis of influenza A H1N1 strains (\*). For influenza A H3N2 or influenza B, oseltamivir or zanamivir can be used. If the strain of influenza is unknown, currently, zanamivir by itself or a combination of oseltamivir and rimantadine is appropriate coverage (3). Resistance to zanamivir remains rare. Zanamivir is not recommended for patients with reactive airway disease, because it may exacerbate bronchospasm. Future influenza treatment and prophylaxis recommendations for influenza will need to be guided by close monitoring of CDC reports on influenza resistance patterns. Treatment should begin < 48 h after onset of symptoms (Table 1). In practice, physicians are often faced with the question of whether to treat patients who present outside the 48-h period. At present, only one observational study addresses this question in hospitalized adults (12). In 327 adults hospitalized with influenza, mortality was significantly lower in those who received antiviral treatment as compared to those who did not receive antiviral treatment. Of the 100 patients who were treated, only 29% had symptoms < 48 h.

## Prevention

The cornerstone of reducing the morbidity and mortality of influenza in the elderly is vaccination (see also chapter “Vaccinations”). Although the degree of protective efficacy for current inactivated vaccines in the elderly has recently become a subject of controversy, older adults clearly benefit from vaccination (13). A multi-layered approach for protecting the elderly from influenza is needed and includes vaccinating elderly persons, their close contacts and care givers, and providing oseltamivir if exposure to influenza has been documented (3, 14). When staff was highly vaccinated, several studies have demonstrated a benefit to elderly residents of LTCFs (15). The recommendations of the Advisory Committee on Immunization Practices (ACIP) 2007 relating to the elderly, include vaccination of all persons  $\geq 50$  years, vaccination of residents of nursing homes and chronic-care facilities, vaccination of healthcare personnel, and vaccination of healthy household contacts (including children) and caregivers of adults  $\geq 50$  years (3).

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\* [http://emergency.cdc.gov/coca/ppt/Antivirals\\_update\\_010809\\_Fiore.pps](http://emergency.cdc.gov/coca/ppt/Antivirals_update_010809_Fiore.pps)

At the present time, only trivalent inactivated virus (TIV) vaccine, which contains killed H1N1, H3N2 and B strain influenza, is recommended for use in persons 50 years and older (3). Mild acute local reactions occur in approximately one-third of vaccines and systemic reactions such as fever, and myalgias are uncommon in older persons. Influenza vaccine may be safely given simultaneously with pneumococcal vaccine, and the only contraindications to vaccination are anaphylactic hypersensitivity to eggs or other components of the vaccine and a history of Guillian–Barré syndrome. By using adjuvants and higher doses of antigens, active research continues to improve the immunogenicity and efficacy of inactivate influenza vaccine. Live attenuated influenza virus vaccine is not approved for persons over age 49; however, it may be given to healthcare workers and close household contacts of older adults.

Antiviral prophylaxis is recommended for all residents of nursing homes and chronic care facilities and to unvaccinated healthcare providers once influenza A has been documented in the institution (13, 14). Chemoprophylaxis is given regardless of vaccination status and is continued until 1 week after the onset of the last influenza case.

## ***Respiratory Syncytial Virus***

### **Epidemiology and Clinical Relevance**

RSV has long been recognized as the leading cause of lower respiratory tract disease in children; however, recently, it has been recognized as a serious adult pathogen (16). It is estimated that RSV results in approximately 178,000 hospitalizations and 14,000 deaths annually in the United States yielding healthcare costs in excess of \$1 billion. A number of epidemiologic studies and mathematical models indicate that RSV is second to influenza as a cause of serious viral respiratory disease in adults (7).

RSV was initially recognized as a pathogen in older persons when several outbreaks were described in long-term care facilities (17). Attack rates are variable and may be as high as 90% during outbreaks, but more commonly they range from 1 to 7% when residents are followed prospectively. In published reports, rates of pneumonia range from 0 to 53% and death from 0 to 55%. RSV appears to cause serious disease in community-dwelling older persons as well. In a 2-year prospective study of elderly persons in the United Kingdom (UK) Nicholson et al., identified RSV in 3% of illnesses using serology for diagnosis (18). With the advent of sensitive molecular testing, a more accurate assessment of the true incidence of RSV has emerged. In a 3-year study from the United Kingdom by Zambon et al., RSV was identified by RT-PCR in 10–18% of adults age 65 years and older who were visiting a general practitioner during the winter for a respiratory illness (19). In comparison, during the same period, influenza A was identified in 13–42% of subjects. In a prospective study from Rochester, NY, using a combination of viral culture, RT-PCR and serology for diagnosis, RSV infection was documented in 3–7% of 608 healthy elderly and 4–10% of adults with chronic cardiopulmonary conditions

over four winter seasons (16). Serious disease was more common in high-risk patients: 9% visited the Emergency Room, 16% required hospitalization, and 4% died. Finally, a large study of community-acquired pneumonia in adults found RSV to be the third most commonly identified pathogen at 4.4% compared with 6.2% due to *Streptococcus pneumoniae* and 5.4% due to influenza (20).

### **Clinical Manifestations**

Manifestations of RSV infection can be difficult to distinguish from other viral respiratory infections, particularly influenza. Most individuals with RSV have nasal discharge, cough, sputum production, and constitutional symptoms. Although overlap exists, there are some helpful clues to differentiate RSV from influenza. High fever, sore throat, myalgias, and gastrointestinal complaints are more characteristic of influenza, whereas rhinorrhea, dyspnea, sputum production, and wheezing are more frequently associated with RSV infection.

### **Diagnostic Tests**

Unfortunately, because of the labile nature of the virus and low titers of virus in nasal secretions in adults, diagnosis of acute RSV by standard testing is difficult. Under ideal circumstances, viral culture is only 50% sensitive when compared with serology using EIA. Commercial rapid antigen tests also have poor sensitivity in adults (21). RT-PCR offers the best combination of sensitivity and specificity for the diagnosis of acute RSV in adults but is not widely available to most clinicians.

### **Treatment**

The treatment of RSV infection in adults is largely supportive. Supplemental oxygen and bronchodilators may be useful, and antibiotics should be considered if bacterial super-infection is suspected. Ribavirin is a nucleoside analogue, which has broad antiviral activity, including RSV. Anecdotal experience suggests it may be beneficial in selected cases, particularly in persons with immunosuppression. However, due to lack of data in the elderly, general recommendations on its use cannot be made (22). The major problems with ribavirin are its high cost and difficulty with administration. The recommended 12–18 h/day of aerosol at 20 mg/mL concentrations may be quite difficult for the elderly adult to tolerate. Higher concentrations (60 mg/mL) given three times a day may also be effective and more tolerable (23).

### **Prevention**

In healthy elderly patients and in adults with chronic pulmonary disease, low serum neutralizing antibody titers are associated with increased risk of hospitalization with RSV infection suggesting a vaccine may be beneficial. Although research is

ongoing, an effective RSV vaccine has yet to be developed. RSV is spread primarily by large droplet inoculation and fomites, and handwashing is the single most important measure in the control of RSV.

## *Parainfluenza Viruses*

### **Epidemiology and Clinical Relevance**

The parainfluenza viruses (PIV) are most commonly thought of as the etiologic agents of croup, bronchiolitis, and pneumonia in young children (24). Four serotypes and two subgroups of PIV are recognized (1, 2, 3, 4a, and 4b); PIV-3 is endemic throughout the year, whereas PIV-1 and PIV-2 tend to occur during the fall. Although PIV infections are not commonly documented in older adults, several studies of community-acquired pneumonia and chronic obstructive pulmonary disease (COPD) exacerbations implicate PIV as a cause in 2–17% of cases (25, 26). The PIV-1 and 3 serotypes account for the majority of isolates in older persons, with PIV-2 being relatively uncommon (27).

### **Clinical Manifestations**

Similar to RSV, outbreaks of PIV infections in nursing homes have been described (27, 28). Variable morbidity and mortality has been reported. Clinical characteristics of PIV infection are not distinctive and include rhinorrhea, sore throat, hoarseness, and cough with high rates of pneumonia ranging from 20 to 30%. In an institutional outbreak of PIV-3, the attack rates among residents and nursing staff were 31% and 11%, respectively. Antecedent parainfluenza infection in long-term care residents has been linked to outbreaks of pneumococcal pneumonia.

### **Diagnostic Tests and Treatment**

In clinical practice, a diagnosis of PIV infection is usually made by viral culture, although RT-PCR is available in some settings (24). Diagnosis can also be made serologically; however, PIV-1 and 3 infections result in cross-reactive antibody responses and cannot be distinguished. No antiviral agents have been approved for the treatment of PIV infection.

## *Human Metapneumovirus*

In 2001, human metapneumovirus (hMPV) was first identified in the Netherlands from archived respiratory cultures collected from infants and young children in whom other pathogens could not be isolated (29). It is an enveloped RNA virus

closely related to RSV and PIV. Since its discovery, infection has been widely reported each winter in young infants with an illness similar to RSV and characterized by wheezing and bronchiolitis (30). However, as with many pediatric respiratory viral pathogens, hMPV infection induces incomplete immunity and reinfections occur later in life at all ages (31, 32).

### **Epidemiology and Clinical Relevance**

In a 2-year study, hMPV infection was identified in 4.1% of elderly and high-risk adults, using RT-PCR and serology for diagnosis (32). Impact was greatest in subjects with cardiopulmonary diseases, who were ill twice as long as healthy elderly. In a study of adult pneumonia, 4% of subjects were diagnosed by RT-PCR with hMPV (33). Seventy-five percent of those infected were 65 years of age and older. Such hMPV outbreaks can also occur in LTCFs. In a recent outbreak of severe hMPV illness in an LTCF in Quebec, Canada, 17% of those infected had pneumonia and 50% died (31). Autopsy material from an elderly woman with an extensive right middle and lower lobe pneumonia confirmed the presence of virus in the lower airways by immunohistochemical staining. The clinical characteristics of hMPV pneumonia in older adults do not appear to be distinctive from the other wintertime respiratory viruses. Cough is universal and wheezing, dyspnea, and sputum production are common symptoms (32).

### **Diagnosis and Treatment**

In part due to its fastidious growth characteristics, hMPV remained undetected for many years. Although isolation by viral culture is possible, this method of diagnosis is not practical, and RT-PCR is the diagnostic method of choice (30). Rapid tests have been developed for direct antigen detection in respiratory secretions; however, there are little data regarding sensitivity in the elderly. Currently, there is no known effective antimicrobial therapy against this virus. Therapy is primarily symptomatic, supportive, and managing any complications.

## ***Rhinoviruses***

### **Epidemiology and Clinical Relevance**

Rhinoviruses are the most commonly identified cause of the “common cold,” accounting for 25–50% of upper respiratory infections (34). Rhinoviruses circulate at all times of the year, but peak activity tends to be during the spring and fall. Because the virus does not replicate well at 37°C, infection of the lower airways was previously considered rare. However, recent studies utilizing experimental

challenge and specimens obtained at bronchoscopy clearly demonstrate rhinovirus infection of the lower respiratory epithelium (35).

A prospective study from the United Kingdom indicates that rhinoviruses are an important cause of debility and lower respiratory disease in elderly people in the community (36). Rhinoviruses accounted for 24% of respiratory illnesses in a cohort of 533 persons over a 2-year period. Although death and hospitalization rates were low, the mean length of illness was 16 days, and 26% of people were unable to perform their normal household activities. The presence of chronic medical conditions and smoking increased the likelihood of lower respiratory tract complications. Because of the frequency of rhinovirus infection, the overall burden of disease in the elderly may approach influenza. Rhinovirus has also been identified as the cause of 3.1%–19.6% of COPD exacerbations (37). Lastly, outbreaks of severe respiratory illness due to rhinovirus have been described in nursing homes with attack rates as high as 56% and a mortality as high as 21% of those affected (38, 39).

### **Clinical Manifestations**

In elderly persons, nasal congestion (79–89%), cough (71–94%), constitutional symptoms (43–91%), and sore throat (21–51%) characterize illnesses. Rhinoviruses are now appreciated as a common trigger for asthma exacerbations and, therefore, in persons with preexisting lung disease, the dominant symptom may be wheezing (34).

### **Diagnostic Tests and Treatment**

The diagnosis of rhinovirus is usually made by a viral culture of nasopharyngeal secretions. If available, the use of RT-PCR greatly increases detection rates (34). Treatment is supportive and care should be exercised when prescribing “cold” medications to elderly persons because many of these “cold” medications contain combinations of sympathomimetics and antihistamines.

## ***Coronaviruses***

### **Non-SARS Coronaviruses**

Coronaviruses are RNA viruses of which two are major serotypes: human coronavirus 229E (HCo-229E) and HCo-OC43, which, for decades, have been known to cause respiratory disease in humans (34). Two recently discovered coronaviruses (HCo-NL63 and HCo-HKU1) cause lower and upper respiratory tract infections with similar frequency (40–42). In temperate climates, peak viral activity occurs in

the winter. Reinfections with coronaviruses are common throughout life, and, similar to rhinoviruses, illnesses are generally mild upper respiratory infections in healthy adults; symptoms include malaise, headache, sore throat, and nasal congestion. Exacerbations of chronic obstructive pulmonary disease have been linked to coronavirus infections in several studies.

Coronavirus infections have been evaluated in the community-dwelling elderly and have, in one prospective study from the United Kingdom, accounted for 9.5% of the respiratory illnesses (18). Coronavirus's were associated with lower respiratory tract symptoms in more than 40% of cases; infections have also been documented in LTCFs and in frail elderly people attending daycare centers (43). Coronaviruses have also been implicated in severe respiratory infections requiring hospitalization in older adults (44). RT-PCR is now available for diagnosis of coronavirus infection but frequently a specific viral diagnosis is not made (34). No antiviral agents are available, and treatment is supportive.

## Hepatitis Viruses

### *Hepatitis A*

Hepatitis A virus (HAV) is an RNA virus in the picornavirus family (see Table 2). The virus is easily transmitted by the fecal–oral route. In countries where the virus is endemic and sanitation is poor, most people become infected in early childhood when the disease is mild and life-long immunity results (45). Recently, a shift in the prevalence of cases from childhood to adulthood has occurred, presumably due to improved living conditions. The incidence of hepatitis A in the United States has fallen 88% from a peak in 1996 to an all-time low of presently 1.2 cases per 100,000 persons (46). The prevalence of anti-HAV antibodies increases with advancing age (47). In a 1994 study from Colorado, the prevalence of anti-HAV antibodies at ages 60, 70, and 80 was 40%, 60%, and 80%, respectively (45).

**Table 2** Viral hepatitis

Virus	Transmission	Incubation range in days (average)	Clinical characteristics in older persons	Chronic infection
A	Fecal–oral	14–50 (28)	Prolonged cholestasis	No
B	Parenteral, sexual	45–160 (120)	Milder acute infection, but chronic infection more common. Sequelae: cancer and cirrhosis	Yes
C	Parenteral, other?	15–150 (42)	Same as hepatitis B virus (HBV)	Yes
D	Parenteral, sexual	45–130	May worsen existing cirrhosis from HBV	Yes
E	Fecal–oral	14–60	No data	No
G	Parenteral	Limited data	Clinical significance unknown	Yes



An acute hepatitis A, advancing age correlates with more severe clinical manifestations, higher bilirubin levels and increased hospitalization rates (48). Liver failure and death are also more common with increased age (49). In the United States, the overall case fatality rate for HAV infection is 0.3%; however, it rises to 1.5% in persons 60 years or older (46).

An inactivated hepatitis A vaccine has been available since 1993, and clinical studies have shown the vaccine to be safe, very well tolerated, and highly immunogenic in all age groups. Immunization of toddlers in Israel resulted in a >95% reduction of hepatitis A in the general population (50). Although the benefit was least for ages  $\geq 65$  years, a 77.3% reduction in cases was observed in this age group. Immunogenicity in frail elderly persons such as residents of long-term care has not been reported. Although disease may be more severe in older adults, current vaccination policies do not specifically target the elderly. However, vaccination is recommended for older travelers who plan to visit countries endemic for HAV.

## *Hepatitis B*

Hepatitis B virus (HBV) is a complex deoxyribonucleic acid (DNA) virus transmitted by percutaneous and mucous membrane exposure to infectious body fluids. Serum, saliva, and semen have been shown to contain hepatitis B surface antigen (HBSAg). Since 1990, the incidence of acute hepatitis B has declined in all age groups with the largest decline (98%) being in children <15 years (46). Because the primary risk group in the United States and Europe is intravenous drug abusers, acute infection is not common in the elderly. Transfusion-related HBV infection is now an uncommon event with risk estimated to be 1 in 205,000 transfusions (51). When several outbreaks occurred during the 1970s–1980s, LTCF's were thought to be a risk area for HBV (47). However, recent surveys of geriatric hospitals indicate the prevalence of HBSAg is similar to the general geriatric population (<1%) (47).

Acute HBV in older adults is usually mild, and many cases are subclinical or presents with manifestations of cholestasis. In addition to the typical symptoms of jaundice, anorexia, and fatigue, diarrhea is a common complaint in elderly persons. Complaints reflecting immune complex disease such as myalgias and arthralgias are rare in older adults. Although acute HBV is generally not a severe disease in older adults, the mortality from fulminant HBV increases with age (47). In a multivariate analysis of prognostic factors in 115 patients with HBV, age was an independent predictor of survival (46). Mortality for persons over age 60 years was 3.1% compared with 1.2% for persons ages 40–59. When individuals are infected at older ages, chronic carriage rates also increase. Compared with a 10% carriage rate in young adults, approximately 60% of older persons become chronic carriers (47).

In addition to cirrhosis from chronic active hepatitis, one of the major complications of HBV infection is hepatocellular carcinoma (HCC). The length of time infected is an important factor in the development of cancer, and, thus, elderly persons who have been infected for many years are at the greatest risk. The rate of

HCC rises from 197 per 100,000 in 30- to 39-year olds to 927 per 100,000 in 60- to 69-year-old chronic HBV carriers (52).

Most cases of acute hepatitis B clear spontaneously and do not require treatment. In young patients with compensated disease, alpha-interferon is primarily used in the treatment of chronic hepatitis B. Those who respond favorably may see suppression of viral replication and a decrease in the risk of progression to cirrhosis or to cancer. Side effects of therapy are frequent and increase with advancing age (47). Therapy should be reserved for patients in overall good health, except for their liver disease, and who have evidence of active viral replication. Five nucleotide/nucleoside analogs (lamivudine, adefovir, entecavir, tenofovir, and telbivudine) are currently approved by the Food and Drug Administration to treat chronic hepatitis B (53). These drugs are usually better tolerated than interferon, although they have not been studied specifically in the elderly. Patients with chronic hepatitis B should be tested for immunity to hepatitis A and, if seronegative, should be vaccinated against hepatitis A to prevent acute decompensation that could occur with hepatitis A superinfection. In addition, patients should be counseled to abstain from alcohol, to maintain a healthy body weight, and to use condoms to protect their sexual partners from infection.

The currently licensed hepatitis B vaccine is a genetic recombinant vaccine; it is very well tolerated and highly immunogenic with excellent protective efficacy in children and young adults. However, response rates to HBV vaccine diminish significantly with increased age. Ninety percent of persons under age 40 achieve an adequate seroresponse compared with only 50% in persons over age 60.

## *Hepatitis C*

Hepatitis C virus (HCV) is an RNA virus in the flavivirus family. Exposures to contaminated blood, either through occupation or through intravenous drug abuse, may transmit HCV. Although 40–50% of community-acquired HCV cases do not report a parenteral exposure, nonparenteral transmission of HCV is not well understood. Sexual transmission, if it occurs, is not efficient. The major risk factor for HCV in older persons is transfusion, and most became infected prior to routine screening of the blood supply in 1990 (47). For southern Europe and Japan, the peak era of transfusion-associated HCV was between 1940 and 1960 whereas in the United States and northern Europe, the peak transmission was between 1960 and 1980. The current risk of acquiring HCV from transfusion in the United States is approximately 1 in 1,935,000 (51). In southern Europe, numerous population-based studies have shown that the prevalence of HCV is 16–42% in persons over 60 years and 33–50% in those over 80 years; infection is extremely rare in subjects <40 years (54).

The seroprevalence of 1.4–2.2% in LTCF residents is approximately that of the general elderly population (55). The clinical manifestations of acute HCV are generally mild and nonspecific. In a series of 20 older people with acute non-A

non-B hepatitis, approximately 30–40% had fever, abdominal pain, and jaundice (47). Fulminant hepatitis is rare with HCV, but development of chronic liver disease is very common (56). Virtually all persons become chronically infected, and a significant number develop chronic liver disease. On average, 20 years after initial infection, chronic active hepatitis or cirrhosis develops in 29–76% of persons.

Age affects the rate of progression to cirrhosis in two important ways: The younger a patient is when HCV is acquired, the slower the rate of progression to cirrhosis; however, the longer one is infected, the greater the risk of development of cirrhosis and HCC (54). Hepatocellular carcinoma is clearly associated with chronic HCV infection, and the relative risk of cancer from HCV may be even greater than that from HBV. In a study of 25 older persons with HCV in the United Kingdom, 36% developed HCC (56).

Chronic HCV infection is currently treated with pegylated interferon alpha and oral ribavirin. Goals of therapy include clearance of viremia and prevention of decompensated cirrhosis and HCC. Persons with high viral load and viral genotype 1 have a low response rate to  $\alpha$ -interferon, and, many patients who initially respond, relapse when therapy is discontinued (47). Most studies of interferon treatment of HCV have not included older participants. In one study from Japan, interferon was administered to 19 patients aged 65 and older with HCV, and the response rate was 26% compared with 33% in younger persons (57). Of note, the older subjects had higher HCV–RNA titers and more severe fibrosis on their liver biopsy as compared to their younger subjects. Response rates in elderly persons correlated with lower HCV–RNA titers. Because older persons have more side effects and a lower response rate to interferon, treatment should be carefully considered on an individual basis; it should be proposed only in patients up to 75 years who have a significant risk of progression of liver disease, no serious co-morbidities, and an otherwise good life expectancy (54).

Patients with chronic hepatitis C should be tested for immunity to hepatitis A and B and, if seronegative to either, they should be vaccinated to prevent acute decompensations that could occur with hepatitis A or B superinfection. They should be counseled to abstain from alcohol, to maintain a healthy body weight, and to use condoms to protect their sexual partners from infection.

## Gastroenteritis Viruses

Although deaths related to diarrhea have traditionally been thought to be a problem of young children in developing countries, in the United States from 1979 to 1987, 51% of the 28,538 diarrhea-related deaths occurred in adults over the age of 74 as compared to 11% in children <5 year old (58). The odds ratio of dying during a hospitalization involving gastroenteritis was 52.6 for adults over the age of 70 as compared with children less than 5 years of age. Residents of nursing facilities are at particular risk for infectious diarrhea illness because of the outbreaks that can occur in closed populations. The majority of nursing facility outbreaks of gastroenteritis are probably viral and

include rotavirus, enteric adenoviruses, norovirus, Snow Mountain agent, and small round structured viruses (SRSV) (58, 59).

Rotaviruses are small RNA viruses in the retrovirus family and are the most important cause of gastroenteritis in infants and young children worldwide. The mode of transmission is assumed to be fecal-oral, and the virus is relatively resistant to common disinfectants and facilitating nosocomial dissemination. Several outbreaks of rotavirus infection in elderly residents of LTCFs have been reported with attack rates ranging from 36 to 66% and mortality rates of 1–10% (60, 61). A typical illness lasts 2–3 days and includes voluminous vomiting and watery diarrhea with low-grade fever. Death may result from dehydration progressing to oliguria and acidosis (60, 61). In an analysis of specimens from gastroenteritis outbreaks in aged care facilities in Australia, rotavirus was detected by electron microscopy in 18 of 29 individuals in 7 out of 53 outbreaks (62). Although rotavirus infections are most common in winter, outbreaks can occur at other times of the year (63).

Rotavirus serum antibody titers offer some protection against severe disease and tend to diminish with increasing age (61). Two rotavirus vaccines were released in 2006 for use in children, a pentavalent human-bovine reassortant rotavirus vaccine called RotaTeq<sup>®</sup> and a live-attenuated human rotavirus vaccine called Rotarix<sup>®</sup>. No data on safety or immunogenicity in the elderly exists; however, given the mortality rates in this age group, further study would be reasonable.

Norovirus (formerly called Norwalk-like virus) is also a frequent cause of diarrhea in adults including the elderly (see also chapter “Infectious Diarrhea”). In a study of 20 gastroenteritis outbreaks in Maryland, 52% of stool samples were positive for Norwalk-like virus (NLV) (64). The median duration of symptoms with NLV gastroenteritis is 2–3 days (65).

## Herpes Virus Infections

### *Varicella Zoster*

Varicella-zoster virus (VZV) is a DNA virus and a member of the herpes virus family. It causes two distinct clinical syndromes: primary disseminated infection (chickenpox) and reactivation of latent virus in the dorsal root ganglia, leading to herpes zoster or “shingles” (66). Herpes zoster is a painful, vesicular exanthem that erupts in one to two dermatomes after a prodrome of days to weeks and may take up to a month to heal. Most patients report a deep aching or burning sensation, altered sensation to touch with paresthesias, dysesthesia, or hyperesthesia. Herpes zoster is a common condition with a cumulative lifetime incidence of 20–30% with most of the risk concentrated in older age. The overall incidence is 1.2–3.4 per 1,000 person-years, but rates rise sharply with increasing age to 11.8 per 1,000 for persons age 65 years and older (67). Chapter “Herpes Zoster” is devoted to the topic of herpes zoster, and the reader is referred to this section for further details.

## Epstein–Barr Virus

The Epstein–Barr Virus (EBV) is a herpes virus that establishes lifelong infection. Primary infection may occur in childhood when infection is asymptomatic or during adolescence when the symptoms of classic mononucleosis are most often observed (66). Although primary infection is uncommon in old age, the manifestations may be different than those in youth, which makes diagnosis challenging. Seroepidemiologic studies indicate that 3–10% of older adults are at risk for primary infection (66). Diagnosis is also often delayed because symptoms may be misleading. Lymphadenopathy, pharyngitis, and splenomegaly are significantly less common and jaundice is more common in older persons as compared with the young persons (67). Fever is more common and often lasts more than 2 weeks (68, 69). The neurologic manifestations of EBV infection are protean, and acute EBV encephalitis has been described (70). Adding to the difficulty of making a correct diagnosis, development of atypical lymphocytosis may be absent or delayed in the elderly. Diagnosis of primary EBV is made by the presence of heterophile antibodies or EBV-specific IgM. Although acyclovir has in vitro activity against EBV, no benefit has been demonstrated in the treatment of acute EBV infection.

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**Part III**  
**Unique Infectious Disease**  
**Problems**

# Infections in the Long-Term Care Setting

Suzanne F. Bradley

## Key Points

In the long-term care setting

- The diagnosis of infection is primarily based from the clinical assessment.
- Infection is a common cause of fever, when present, and acute change in functional status.
- Infection can often present atypically; usual symptoms, physical findings, and diagnostic abnormalities may be lacking.
- Evaluation of fever and suspected infection should initially focus on the most common clinical syndromes.
- Treatment should initially focus on the most common organisms that are present at the most likely suspect site of infection.

## Significance of Infection in the Long-term Care Setting

In the past, infections in long-term care facility (LTCF) were thought to have been as common as those in hospital, but less severe (1). LTCFs were regarded as healthcare facilities that provided skilled care for an indefinite period of time predominantly for elderly patients who were no longer able to live independently. Resources in LTCFs were limited; patients with infections were frequently transferred to a hospital for diagnostic evaluation, intravenous treatment, and monitoring (1, 2). As the role of the typical nursing home (NH) within our healthcare system has evolved, this perception of LTCF's may be changing.

The acuity of the typical "modern" LTCF patient is increasing, as patients are now discharged from hospital to continue treatment for increasingly complex conditions and undergoing rehabilitation prior to being discharged home (1, 3). For example,

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a significant proportion of patients may have indwelling devices that may predispose the patient to infection. With the expansion of rehabilitative, subacute care, and acute-chronic care services, more chronic care facilities are providing a wider range of services for an increasingly ill patient population (1, 4). In this current environment, it is likely that the number, complexity, and severity of infections cared for in LTCF will continue to increase.

In contrast with the acute-care hospital setting, our understanding of the prevalence of infection within the chronic care setting remains relatively scant. Most studies of the chronic care setting primarily describe the typical skilled nursing facility experience that was described above. As a result, this discussion will be limited primarily to skilled nursing facilities/nursing homes, referred to in general as LTCFs.

## How Common are Infections in LTCFs?

The prevalence of infection in skilled nursing or LTCFs has been reported to range from 1.8 to 13.5 infections per 1,000 patient-care days with an associated mortality ranging from 0.04 to 0.71 per 1,000 resident-days (1). It is thought that the wide-range of infection rates may reflect the diversity of populations that require chronic inpatient care. Infections of the urinary and respiratory tracts are most commonly followed by skin and soft tissue infections (SSTI); these three clinical syndromes account for the majority of infections seen in the chronic care setting (1–3, 5). Gastrointestinal (GI) and bloodstream infections (BSI) are less frequently documented and, perhaps, are less prevalent (3). Cultures of blood have not been recommended in part because BSI are perceived to be uncommon; when present death occurs rapidly, and most residents transferred to hospital before the diagnosis of BSI can be made or advanced directives preclude evaluation (2, 6).

The prevalence of specific infectious agents in LTCFs is uncertain. The frequency of infections reported is biased by the ease of specimen collection, diagnostic testing, and the likelihood that the results will alter treatment. The most prevalent infection, urinary tract infection (UTI), is also the most often over-diagnosed clinical syndrome, as cultures of urine are easily obtained and positive results are frequent even in the absence of symptoms (7, 8).

In contrast, the causes of lower respiratory tract infections (LRTI) frequently escape detection. Collection of sputum for culture is difficult; specimens may be collected in <30% of LTCF residents with pneumonia and half of them may be inadequate. Many common, but fastidious, bacterial respiratory pathogens may not grow on routine culture and diagnostic testing, for most viruses are not readily available or sensitive (2, 9–11). Without culture of blood or tissue, the etiology of SSTI is rarely known, and differentiation between infection and superficial colonization is difficult (12, 13). Diarrhea is also a common cause of infection in LTCFs and often self-limited unless *Clostridium difficile* is suspected, care is generally supportive. With the exception of *C. difficile*, fecal samples are rarely tested for viruses, as these tests are generally not available and parasites and other bacterial etiologies are relatively uncommon as causes of LTCF-associated diarrhea (2, 14, 15).

The organisms that cause common clinical syndromes in LTCF will be discussed under each entity below. Other mitigating factors that can influence the prevalence of microorganisms, specifically within the LTCF, such as the prevalence of device use, acquisition in hospital prior to admission, antecedent use of antibiotics, and the state of the host immune system, will also be discussed.

In general, antibiotic-resistant bacteria emerge and thrive in environments such as hospitals and intensive care units where the selective pressure of antibiotic use is the most intense. Colonization with antibiotic-resistant bacteria is common in the LTCF setting (1). An important area of investigation is predicting which residents who are colonized with resistant bacteria will develop infection (16).

## Clinical Manifestations

Residents with impaired cognitive or communication abilities may not be able to provide a reliable history. Aging, comorbid illness, and medications may impair the host inflammatory response, leading to blunting of focal symptoms and physical findings. Thus, detection of infection by history and physical examination in LTCF residents can be especially difficult; findings suggestive of a specific clinical syndrome may be subtle or absent. In LTCF residents with other non-infectious illnesses, the significance of abnormalities noted on physical or laboratory examination may be misinterpreted. Changes in symptoms and signs associated with specific clinical syndromes will be discussed under those topics.

A more generalized approach is necessary to detect infection in LTCF residents. Acute or worsening changes in the ability to perform basic activities of daily living such as toileting, mobility, dressing, or feeding can be a very sensitive indicator for infection in LTCF residents. Fever can be a very useful indicator if its definition is sufficiently sensitive to detect most infections in the population being evaluated. The most common definition of fever (temperature  $>101^{\circ}\text{F}$ ) is met in only 40% of LTCF residents. If the fever definition in this population is lowered to  $100^{\circ}\text{F}$  ( $37.8^{\circ}\text{C}$ ), then 70% of infections will be detected with a specificity of 90%. More than half of NH residents with a temperature of  $100^{\circ}\text{F}$  will have infection. Other investigators have suggested that baseline temperatures should be established for each resident; fever would be defined as an increase of  $2^{\circ}\text{F}$  ( $1.1^{\circ}\text{C}$ ) over the baseline temperature or  $>99^{\circ}\text{F}$  ( $37.2^{\circ}\text{C}$ ) orally or  $99.5^{\circ}\text{F}$  ( $37.5^{\circ}\text{C}$ ) rectally (2, 5, 17). Signs of dehydration such as decreased oral intake, dry mucous membranes and tongue, or furrowed tongue may, indirectly, be an indicator that fever and possible infection is present in this population (2, 5).

## Diagnosis

Often mentioned criteria for infection were primarily developed as a tool for retrospective infection detection for surveillance purposes, rather than for diagnosis. Criteria from the Centers for Disease Control and Prevention (CDC) were derived from the acute-care experience and rely heavily on laboratory results and diagnostic procedures. Alternate

definitions for LTCF have been sought. The McGeer criteria were developed specifically for LTCFs and rely primarily on readily available clinical criteria derived from history and physical examination (see Table 1) (18). The Minimum Data Set was developed to document resident problems on a quarterly basis during their LTCF stay, but recent studies suggest that this is not a reliable instrument for diagnosis of infection (19, 20).

**Table 1** McGeer et al. criteria – adapted from definitions for infection surveillance in long-term care facilities: Reference (18)

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General principles

All symptoms must be new or worsening

Consider non-infectious etiologies before making the diagnosis

Identification of infection should not be based upon one piece of evidence.

Urinary tract infection

Only symptomatic bacteriuria is included

No indwelling urinary catheter and  $\geq 3$  criteria are met:

1. Fever  $\geq 100.4^{\circ}\text{F}$  ( $38^{\circ}\text{C}$ ) or chills
2. New or increased dysuria, frequency, or urgency
3. New flank or suprapubic pain or tenderness
4. Change in character of the urine<sup>a</sup>
5. Worsening of mental or functional status

Indwelling catheter and  $\geq 2$  criteria are met:

- (a) Fever  $\geq 100.4^{\circ}\text{F}$  ( $38^{\circ}\text{C}$ ) or chills
- (b) New flank or suprapubic pain or tenderness
- (c) Change in character of the urine<sup>a</sup>
- (d) Worsening of mental or functional status

Pneumonia

Non-infectious causes must be ruled out

Both of the following criteria must be met:

1. Chest radiograph demonstrating definite or probable pneumonia or a new infiltrate
2.  $\geq 2$  other symptoms of lower respiratory tract infection
  - (a) New or worsening cough
  - (b) New or increased sputum production
  - (c) Fever  $\geq 100.4^{\circ}\text{F}$  ( $38^{\circ}\text{C}$ )
  - (d) New or increased physical findings (rales, rhonchi, wheezes)
  - (e) At least *one* indication of breathing difficulty
    - (1) New or increased respiratory rate  $>25$  breaths per minute
    - (2) Worsening mental status
    - (3) Worsening functional status

Cellulitis/skin and soft tissue infection

One of the following criteria must be met:

1. Pus present at a wound, skin, or soft tissue site
2. Presence of *four* or more clinical manifestations:
  - (a) Temperature  $>100.4^{\circ}\text{F}$  ( $38^{\circ}\text{C}$ ) or worsening mental/functional status *and/or at the affected site*:
    - (b) New or worsening warmth
    - (c) New or increasing erythema
    - (d) New or worsening swelling
    - (e) New or increasing tenderness or pain
    - (f) New or increasing serous drainage

Mucocutaneous fungal infection

Both criteria must be met:

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(continued)

**Table 1** (continued)

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1. Maculopapular rash
2. Physician diagnosis or positive smear for yeast
Herpetic infections (varicella zoster and simplex)
<i>Both</i> criteria must be met:
1. Vesicular rash
2. Physician diagnosis or positive viral culture or direct fluorescent antibody test
Conjunctivitis <sup>b</sup>
<i>One</i> of the following criteria must be met:
1. Purulence from one or both eyes for >24 h
2. New or increased conjunctival redness for ≥24 h
Scabies
<i>Both</i> of the following criteria must be met:
1. Maculopapular rash and/or pruritic rash
2. Physician diagnosis or positive microscopic examination
Gastroenteritis
Rule out non-infectious causes such as medications
<i>One</i> of the following criteria must be met:
1. ≥2 loose or watery stools above what is normal within 24 h
2. ≥2 episodes of vomiting within 24 h
3. Both of the following:
(a) At least <i>one</i> symptom compatible with a gastrointestinal infection (nausea, vomiting, abdominal pain, diarrhea)
(b) Positive stool toxin for <i>Clostridium difficile</i> or culture for an enteric bacterial pathogen

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<sup>a</sup>Urinalysis – new pyuria and hematuria in a patient with a previously negative test, observation – new gross hematuria, foul odor, sediment

<sup>b</sup>Symptoms must not be due to allergy or trauma

Few studies have assessed what laboratory procedures are useful in establishing the diagnosis of infection in LTCF residents. A complete blood count (CBC) is a useful diagnostic test to obtain in this setting. Evidence of leukocytosis and or left shift provides strong evidence that an older adult has an infection as defined as a white blood cell count >14,000 cells/mm<sup>3</sup>, neutrophils >90%, or elevated total band count >6% or >1,500 cell/mm<sup>3</sup> (2). Suspicion of dehydration may be supported by the presence of hypernatremia and prerenal azotemia; 60% of LTCF residents may have at least one of these chemical abnormalities (2). Abnormalities of the complete blood count and serum chemistry can provide important clues that infection is present.

## General Principles of Antimicrobial Treatment and Prophylaxis in the LTCF Resident

The need to start antibiotic therapy should be based on the patient's clinical condition; all LTCF patients do not require urgent treatment. Minimum clinical criteria required to initiate empirical antimicrobial therapy for infection have been developed based on expert opinion (21). The burden of evidence for infection required to start

antibiotic treatment is stratified by the presence of risk factors (e.g., devices), severity of symptoms, and presence of underlying diseases such as chronic obstructive pulmonary disease (COPD) (see Table 2).

If urgent treatment is needed, then the empirical choice of antimicrobial should be based on the most likely clinical syndrome and the most likely organism causing an infection at that site. The prevalence of pathogens and their antimicrobial susceptibilities do vary with institutional and geographic factors. Consultation with

**Table 2** Minimum criteria for the initiation of antibiotics in residents of long-term care facilities: Adapted from (21)

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Urinary tract infection

No indwelling urinary catheter:

1. Acute dysuria *alone*
2. Fever  $\geq 100^{\circ}\text{F}$  ( $37.9^{\circ}\text{C}$ ) or  $2.4^{\circ}\text{F}$  ( $1.5^{\circ}\text{C}$ ) above baseline plus  $\geq$  one of the following:
  - (a) New or worsening urgency
  - (b) Frequency
  - (c) Suprapubic pain
  - (d) Gross hematuria
  - (e) Costovertebral angle tenderness
  - (f) Urinary incontinence

Indwelling urinary catheter:

1.  $\geq$  One of the following criteria must be met:
  - (a) Fever as defined above
  - (b) New costovertebral angle tenderness
  - (c) Rigors
  - (d) New onset of delirium as defined by the DSM IV

Respiratory tract infections

1. Fever  $>102^{\circ}\text{F}$  ( $38.9^{\circ}\text{C}$ ) *and*  $\geq$  one of the following
  - (a) Respiratory rate  $> 25$  breaths per minute
  - (b) Productive cough
2. Fever  $>100^{\circ}\text{F}$  ( $37.9^{\circ}\text{C}$ )  $\leq 102^{\circ}\text{F}$  ( $38.9^{\circ}\text{C}$ ) *with* cough *and*  $\geq$  one of the following:
  - (a) Pulse  $> 100$  beats per minute
  - (b) Delirium (DSM IV criteria)
  - (c) Rigors
  - (d) Respiratory rate  $> 25$  breaths per minute
3. Afebrile and high risk COPD (defined as age  $\geq 65$  years)
  - (a) New or worsening cough *and* purulent sputum
4. Afebrile without COPD
  - (a) New cough, purulent sputum *and*  $\geq$  one of the following:
    - Respiratory rate  $> 25$  breaths per minute
    - Delirium (DSM IV criteria)

Skin and Soft Tissue Infection

1. New or increasing purulence at the site of the lesion or wound *or*  $\geq$  two of the following:
    - (a) Temperature  $>100.4^{\circ}\text{F}$  ( $37.9^{\circ}\text{C}$ ) or an increase of  $2.4^{\circ}\text{F}$  ( $1.5^{\circ}\text{C}$ ) over baseline
    - (b) Erythema
    - (c) Tenderness/pain
    - (d) Warmth
    - (e) New or increasing swelling increasing at the affected site
- 

DSM IV Diagnostic and Statistical Manual of Mental Disorder, 4th edition; COPD Chronic Obstructive Pulmonary Disease

the LTCF infection control practitioner and pharmacist can be useful in determining what bacteria and antibiotic resistance profiles are common.

The choice of route for antibiotic administration will be influenced by the severity of the patient's clinical condition, treatment plan, and advance directives. Intravenous (IV) or intramuscular (IM) therapy may be required in the patient with a non-functioning GI tract where absorption of an oral antibiotic is not guaranteed. In the severely-ill LTCF resident who is to remain in the facility and receive IV therapy, broad-spectrum penicillins, second- and third- generation cephalosporins, and carbapenems treat a wide array of beta-lactam-susceptible streptococci, methicillin-susceptible *Staphylococcus aureus*, and aerobic and anaerobic gram-negative bacilli (GNB). Enterococci are not generally susceptible to cephalosporins. Some penicillins cannot be given intramuscularly because of the large doses required and pain with infection; use of broad-spectrum penicillins and some carbapenem antibiotics can be limited by their frequent dosing intervals. If the patient is penicillin-allergic or antibiotic-resistant bacteria are a concern, then treatment with a combination of antibiotics may be necessary.

Treatment should be altered once organisms are identified and antimicrobial susceptibilities are available. Duration of therapy is based on the presumed clinical syndrome to be treated and the organism isolated. Oral therapy can be considered for some clinical syndromes and pathogens, especially if the medication is 100% bioavailable (e.g., fluconazole, linezolid), the patient is clinically stable, and the patient has a functional GI tract. Cost, drug interactions, and toxicity are other factors which should influence the choice of an antibiotic for a LTCF resident. If renal and hepatic dysfunction is present, then adjustments in dose and frequency of administration should be made.

## ***Prevention***

To prevent infection, risk factors must be minimized. Risk of infection may relate to exogenous exposures (other patients, healthcare workers (HCW), or the LTCF environment) or factors intrinsic to the patient (see also chapter "Infection Control Programs in Nursing Homes"). Frequent hand disinfection and adherence to infection control procedures are essential to prevent LTCF-associated infection. Reduction in patient risk factors that contribute to the most common infectious syndromes will be discussed later.

Intrinsic patient factors (underlying disease and debility) frequently lead to presence of extrinsic factors (use of medications and devices) with their side effects and complications. Improvement in function and treatment of comorbid conditions can minimize the use of devices and medications that lead to infection. For example, antimicrobial drugs inhibit and kill the growth of normal flora and allow pathogens to grow. Non-antimicrobial medications can alter the host environment leading to unfavorable growth conditions for normal local flora with subsequent overgrowth of pathogenic flora. Minimizing the use of antibiotics and other unnecessary medications may help prevent infection in LTCF residents. Devices can breach



normal host defenses and allow pathogens to invade and to cause infection. Use of devices contributes to the development of infections of the urinary tract (urethral catheters), respiratory tract (tracheostomy tubes), GI tract (feeding tubes and thermometers), and IV catheters (phlebitis and BSI). To reduce the risk of infection, devices should be removed as soon as they are no longer necessary.

## **Clinical Infectious Syndromes**

In this section, the major focus will be on how the clinical presentation and management of common causes of infection differs in the LTCF. For a more general overview, please refer to specific chapters on each topic.

### ***Urinary Tract Infection***

#### **Epidemiology and Clinical Relevance**

It is not surprising that the urinary tract is the most common source of infection in the LTCF setting (see also chapter “Urinary Tract Infection”). Risk factors that contribute to the development of urinary stasis, in older populations, have been associated with increased rates of bacteriuria (22). Whether urinary stasis alone leads to UTI remains a source of controversy (23). Risk of perineal soiling and urinary contamination by pathogenic bacteria increases in patients with poor functional status who are dependent upon healthcare personnel for toileting. As a result of these factors, a significant proportion of men (15–40%) and women (25–50%) residing in LTCF have bacteriuria and are at risk for UTI (22).

Urinary catheters also introduce potential pathogens into the urinary tract. All residents with a catheter present for more than 30 days will have bacteriuria (24). In a recent nation-wide point prevalence survey of all Veterans Affairs LTCF residents, the indwelling urinary catheter was the most common device in use (3). Residents were 40-fold more likely to have an indwelling urinary catheter than intermittent urinary catheterization; they were also 6-fold more likely to have such a device compared with a suprapubic catheter (3). Residents with an indwelling urinary catheter were significantly more likely to have a UTI (5.5%) as compared with residents without such a device (1.1%) ( $p < .0001$ ). Condom catheters for men have been associated with significantly lower rates of bacteriuria and UTI than indwelling catheters (25).

#### **Etiologic Pathogens**

The pathogens causing UTI in LTCF residents are not predictable; urine cultures and antimicrobial susceptibilities must be obtained. The diversity of urinary pathogens

is due in part to the intense selection pressure of antibiotic use in this setting. It is estimated that 20–60% of all antibiotics used in the LTCF setting are given to treat presumed UTI (26). *Escherichia coli* remains the most common pathogen in women, and *Proteus mirabilis* is more common in men (22). Gram-negative bacilli (GNB) predominate such as *Providencia stuartii*, *Pseudomonas aeruginosa*, *Citrobacter* spp., *Morganella* spp., *Serratia* spp., *Enterobacter* spp., and *Klebsiella pneumoniae* (22). Enterococci, group B streptococci, and *Candida* spp., also cause infection in this setting.

## Diagnosis

Many NH residents will have significant high-grade bacteriuria ( $>10^5$  colony forming units/ml) without symptoms. Pre-emptive trials of treatment for bacteriuria has been shown to be of no benefit in terms of improved well-being, relief of chronic symptoms, prevention of future UTI, or improved survival (7). With the selective pressure of increased antibiotic use, emergence of resistance is inevitable.

Pyuria of any degree does not help differentiate the infected from the uninfected patient, as 30–50% of asymptomatic residents have chronic inflammation as well. It has been known that absence of pyuria strongly correlates with absence of bacteriuria on urinalysis. Urinalysis may not be readily available in most nursing homes; a recent study has shown that use of urine dipstick testing may be an appropriate substitute. If the leukocyte esterase and nitrate are negative, then the possibility of UTI is virtually excluded (27).

There is little diagnostic dilemma if bacteriuria and pyuria are present in addition to typical symptoms and signs referable to the urinary tract such as new or worsening frequency, urgency, dysuria, or flank pain. UTI is a common cause of infection in LTCF residents, but it is rarely a cause of fever (8, 22). These classic symptoms may be lacking particularly in the frail or cognitively impaired patient.

The McGeer et al., criteria require the documentation of significant bacteriuria by culture in addition to new or worsening symptoms. Also, non-infectious causes of nonspecific symptoms such as worsening mental or functional status must also be considered before the diagnosis of UTI is assumed. Asymptomatic bacteriuria should not be treated. These criteria have also stratified definitions for UTI based on the presence or absence of an indwelling urinary catheter (see Table 1). The amount of evidence required for UTI is reduced in the catheterized resident, given that the frequency and severity of infection is greatest among these patients (see Table 1) (18).

To confirm the diagnosis of UTI, the Loeb et al., criteria similarly require the documentation of significant bacteriuria by culture in association with new or worsening symptoms (12). They too agree that asymptomatic bacteriuria, and foul urine, or cloudy urine in the absence of other symptoms, are not sufficient to suspect the diagnosis of UTI or to initiate the use of antibiotics. In the absence of dysuria, the presence of other symptoms such as frequency, urgency, or incontinence requires that a positive urine culture be confirmed to assure that symptoms are likely related

to UTI prior to initiation of antibiotics. The Loeb et al., criteria also lower the quantity of evidence required for the diagnosis of UTI, particularly in residents with indwelling catheters due to their increased risk of severe infection and secondary bloodstream infection (see Table 2) (21). Residents who perform intermittent urinary catheterization are considered to be less likely to have severe UTI - a risk similar to that seen for patients without indwelling catheters (21).

The diagnostic accuracy of criteria developed for the diagnosis of UTI has been prospectively assessed in LTCF residents (28). In general, the McGeer et al., and Loeb et al., criteria were not very sensitive (30%) but were highly specific (79–82%) with a positive predictive value (PPV) (52–57%) and negative predictive value of 60–61%. While more sensitive methods are needed for the diagnosis and treatment of UTI, use of diagnostic algorithms, based on the Loeb et al., criteria, have been shown to reduce unnecessary antibiotic use in LTCFs (29).

## ***Pneumonia/Lower Respiratory Tract Infection (LRTI)***

### **Epidemiology and Clinical Relevance**

Pneumonia is typically the second most common infection in LTCF. Rates of infection vary from 0.3 to 2.5 episodes per 1,000 days of resident care (1, 3). In past years, there have been many risk factors attributed to an increased risk of LTCF-acquired pneumonia, including increasing age, debility, inadequate oral care, swallowing disorders, presence of a feeding tube or tracheostomy, medications that are sedating or reduce gastric-acid, neurological diseases, and many others. Factors that contribute to aspiration appear to be the strongest predictors of pneumonia in LTCF residents (10, 30).

### **Etiologic Pathogens**

Practically speaking, adequate sputum specimens are rare and are obtained in only 5–10% of older adults with suspected pneumonia in the LTCF (2). Therefore, it is difficult to state precisely what organisms are most prevalent in this setting (31). In few carefully performed studies in the LTCF setting, the bacterial causes appear to most closely mirror those seen in older adults in the community rather than those seen in hospitals. *Streptococcus pneumoniae* (13%), aerobic GNB (13%), non-typeable *Haemophilus influenzae* (6.5%), *S. aureus* (6.5%), and *Moraxella catarrhalis* (4.5%) are most common (1, 9, 31). Compared with the acute care hospital, pneumonia due to aerobic GNB is relatively uncommon; when it does occur, *Klebsiella* spp., are the most common genera isolated.

Atypical pneumonia due to *Legionella* spp., *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae* is uncommonly described in LTCFs (31). Influenza and other viruses are common causes of upper respiratory tract infections (URTI) that

can lead to secondary bacterial pneumonia due to pneumococci or *S. aureus* (see also chapter “Viral Infections”). Primary atypical pneumonia due to influenza is uncommon; respiratory syncytial virus, parainfluenza, adenoviruses, coronaviruses, rhinoviruses, and metapneumovirus are rarely diagnosed except during outbreaks because access to laboratories is lacking or the sensitivity of currently available tests themselves is poor (11). Tuberculosis (TB) should be considered in LTCF residents with persistent infiltrates and symptoms that do not respond to conventional antimicrobials, particularly if they involve the upper lobes and if there is a history of prior exposure (32) (see also chapter “Tuberculosis in Older Adults”).

### **Clinical Manifestations**

Typical symptoms of bacterial pneumonia are relatively infrequent among older residents of LTCF. Most will present with some symptom referable to the respiratory tract, but fever may be lacking in almost half of patients with pneumonia. Symptoms such as cough (60–75%), dyspnea (40%), fever (44–65%), and altered cognition (50–70%) are found in LTCF residents with LRTI (2, 9, 31). Less than 60% of residents will present with a classic triad of cough, shortness of breath, or fever (2, 9, 31). New or worsening tachypnea, respiratory rates >25 breaths per minute, is thought to be a sensitive and specific indicator for pneumonia, but some studies have challenged that assumption (33). On physical examination of the LTCF resident, rales may be present less than 60% of the time (2).

### **Diagnosis**

Measurement of oxygen saturation by pulse oximetry can provide additional evidence that pneumonia is likely. In a controlled trial of pulse oximetry in LTCF, residents with pneumonia were significantly more likely to have hypoxemia than residents without pneumonia. A single oxygen saturation of <94% was 80% sensitive and 91% specific for the diagnosis of pneumonia with a PPV of 95%. A decrease in oxygen saturation of 3% from baseline was less sensitive (73%) but more specific (100%) for pneumonia with a PPV of 100% (33).

Oxygen saturation measurements can also assist in decisions to transfer residents with suspected pneumonia to hospital, if allowed by advance directives. Patients with oxygen saturations of < 90% generally require more intensive monitoring available in an acute care setting. When this degree of hypoxemia is coupled with a respiratory rate of >25 breaths per minute, the decision to transfer the resident to acute care must be made quickly, as respiratory failure is imminent (2).

Despite technical difficulties or lack of prior films for comparison, a chest radiograph has been shown to confirm the presence of pneumonia in 75–90% of LTCF residents with pneumonia. It has been suggested that chest radiographs could also provide prognostic information (multi-lobar disease) or evidence of empyema or mass lesions that might alter treatment decisions (2).

The diagnosis of pneumonia should not be made upon an isolated symptom, sign, or finding. For the diagnosis of pneumonia, the McGeer et al., criteria requires that a chest radiograph be done, that evidence for pneumonia or an infiltrate be present, and that other non-infectious causes such as heart failure be excluded. In addition, the patient must also have at least two other symptoms or signs of lower respiratory tract infection, including measures of breathing difficulty (see Table 1) (18).

Despite the difficulties in obtaining sputum from LTCF residents, culture and antimicrobial susceptibilities have been recommended, as the results can help guide therapeutic decisions if the patient is not responding to empirical antibiotic therapy. The presence of antibiotic-resistant bacteria in the facility or uncommon bacteria might alter infection control isolation decisions (2).

Rapid diagnostic tests for respiratory pathogens that do not rely on careful collection of sputum are increasingly available. Urine antigen testing for *S. pneumoniae* and *Legionella pneumophila* serotype 1 has also been proposed, but testing in LTCF populations is limited. During a suspected outbreak of respiratory infection, particularly during winter months, nasopharyngeal swabs for culture and antigen-based testing for viruses may be useful to confirm that an epidemic is present for infection control, and less commonly, treatment and prophylaxis purposes.

If influenza is detected in the facility, then antiviral prophylaxis may be initiated or continued and more intensive infection control measures considered. Use of rapid testing during influenza outbreaks in LTCFs has been associated with reductions in the duration of outbreaks and hospital cost (34). Unfortunately, these antigen-based tests may be only 40–80% sensitive for the detection of influenza (11). The clinician may have to rely on an equally sensitive clinical definition of influenza such as fever and new respiratory symptoms of less than 48 h duration, if rapid testing is negative (35). While diagnostic testing for bacterial and viral pathogens have been recommended as part of an evaluation for pneumonia by an expert panel, there is a need for further evidence that their use will lead to improved outcomes for residents of LTCF (36).

## Management Decisions

Specific antimicrobial treatment is discussed elsewhere. The major focus of this section is devoted to general management issues in the older LTCF resident with pneumonia. There have been a number of recent studies devoted to addressing important decisions, primarily in patients with pneumonia.

If a decision is made to treat with antibiotics, then when should they be started? For the Loeb et al., criteria, the minimum recommended findings required to initiate antibiotic treatment are stratified by amplitude of fever, productive/non-productive cough, and presence of underlying COPD (see Table 2) (21). High fever with tachypnea or productive cough was felt to be a bacterial pneumonia clinically until proven otherwise. For the resident with low fever and non-productive cough, more evidence based on symptoms and signs were required for the initiation of antibiotics.

For high-risk patients with COPD and no fever, new or worsening productive cough was sufficient to initiate antibiotics. For afebrile patients without COPD, non-productive cough for less than 24 h was likely to be due to aspiration and chemical pneumonitis that would not benefit from antibiotics. In addition to these criteria, a CBC demonstrating leukocytosis, and left shift in the setting of fever, might provide more evidence that bacterial infection was present.

Should the patient be treated with antibiotics? In fact, most LTCF patients are treated regardless of the prognosis. In one study, more than half of patients with advanced dementia developed pneumonia within 6 months of death (37). Despite poor prognosis, 91% of patients received antibiotics, 29% were given IV, and 25% were given IM therapy.

If antibiotics are given, then will they be likely to be beneficial? In a multi-center study from Ontario, adherence to published guidelines for antibiotic use in LTCF was uncommon; only 28% of antibiotic courses were appropriate. Even when recommended antimicrobials were given, residents with pneumonia were more likely to die or have adverse reactions than those who did not receive appropriate treatment (38).

Does the route of antibiotic administration affect mortality? When patients from the United States were compared to patients in the Netherlands, U.S. patients with pneumonia were more likely to be hospitalized, receive parenteral antibiotics, and have a lower 1-month mortality (15% vs. 28%) than the Dutch (39). No differences were seen at 3 months, suggesting that an aggressive antibiotic treatment approach confers, at best, a very short-term survival benefit.

What is the effect of antibiotics on the quality of life? LTCF residents with dementia and pneumonia do suffer. The use of oral antibiotics may be associated with less suffering for patients who receive antibiotics vs. those who do not receive them (40).

Do LTCF residents with infection get better care if they are transferred to hospital? There have been several studies suggesting that hospitalization for infection has been associated with a greater reduction in function, development of pressure ulcers, and mortality and development as compared with patients who remain in the nursing home (41).

## **Prevention**

Prevention of pneumonia in LTCF residents should focus on vaccination efforts, prevention of aspiration, and infection control. While influenza vaccine may not prevent influenza illness in LTCF residents, it is highly effective in preventing cardiopulmonary complications, including secondary bacterial pneumonia and death (35) (see also chapter “Vaccinations”).

While there is increasing evidence that prophylaxis with neuraminidase inhibitors is effective in LTCF residents, these drugs are not a substitute for vaccination. Vaccination of healthcare workers has continued to be associated with a significant reduction in influenza infection and in death in LTCF residents (42). While the

efficacy of the pneumococcal polysaccharide vaccination in LTCF residents remains controversial, its use is recommended (43).

The possibility of tuberculosis (TB) as a respiratory pathogen can be reduced through a screening program requiring a baseline chest radiograph and two-step tuberculin skin test for residents upon admission to the facility and annually thereafter (32) (see also chapter “Tuberculosis in Older Adults”). Healthcare workers should be screened upon hiring. More frequent testing may be required and an outbreak investigation initiated if a new case of TB is identified in the LTCF.

Reduction of aspiration risk may be important in pneumonia prevention. Feeding tubes of any kind increase aspiration and pneumonia risk; they should be avoided. It has been proposed that feeding techniques, modified diets, oral hygiene, and positioning strategies be tried first. As a way to prevent overgrowth and colonization with pathogens, elimination of medications that have sedating effects or inhibit gastric acid has also been proposed. Unfortunately, there is little consensus that any strategy to prevent aspiration and pneumonia has been proven to work in the LTCF resident (44, 45).

## ***Skin and Soft Tissue Infection (SSTI)***

### **Epidemiology and Clinical Manifestations**

SSTIs are the third most common infectious clinical syndromes in NH (see also chapter “Skin and Soft Tissues Infections”). Rates of 1–9% [specify for what these rates have been reported] have been reported or a prevalence of 0.5–2.1 per 1,000 patient days (3, 46). Risk factors for SSTI are discussed in more detail elsewhere (chapter “Skin and Soft Tissues Infections”); needless to say, conditions such as peripheral vascular disease and those that contribute to peripheral edema such as chronic venous insufficiency, lymphedema, and immobility, are common in the LTCF resident population. Physical trauma, maceration, pressure, or use of devices allow secondary infection [to do what?] by pathogens found among the resident’s own endogenous flora or exogenously via the hands of personnel, from other residents, or by contact with contaminated environment or fomites (1, 2).

Primary mucocutaneous infections (erysipelas, cellulitis, folliculitis, and impetigo), conjunctivitis, and secondary infection of pressure ulcers are some of the most common manifestations of SSTI seen among LTCF residents. Other common infections include mucocutaneous fungal infections due to *Candida* spp., (thrush, denture stomatitis, chelitis, paronychia, and intertrigo) and dermatophytes (tinea corporis, tinea pedis, tinea cruris and tinea unguium) (47). Rashes, due to ectoparasitic infestations, and reactivation of latent viruses occur as well (12, 13). Many of these common and less severe primary skin infections are not reportable; whether these infections are more prevalent in the LTCF than in the community is not known (12, 13). For some infections, some prevalence estimates are available. For example, it has been reported that ~10,000–20,000 cases of herpes zoster occur in LTCF residents each year. Conjunctivitis is reported in 0.3–3.4% of LTCF residents or at rate of 0.1–1.0 cases per 1,000 resident days (3, 48).

Approximately 6% of pressure ulcers in LTCF residents will become secondarily infected or 1.4 infections per 1,000 resident days (49). The prevalence of pressure ulcers stages II and greater varies widely, likely reflecting the heterogeneity of the resident population; rates range from 1 to 11% (49). Risk of acquiring a pressure ulcer increases with length of stay; ~20% of NH residents will develop an ulcer within 2 years of admission (49–51).

## **Etiologic Pathogens**

### **Primary Skin and Soft Tissue Infection**

Common bacterial causes [for what] include *S. aureus* and beta-hemolytic streptococci, especially group A (2). Mucocutaneous fungal infection is most commonly caused by *Candida* spp., particularly *C. albicans*, and dermatophytes (47), while viral etiologies include those causing herpes zoster and herpes simplex (13). The ectoparasites scabies (*Sarcoptes scabiei*) and head, body, and pubic lice (*Pediculus humanus capitus*, *P. humanus corporis*, and *Phthirus pubis*) may also be found (13).

### **Conjunctivitis**

Most cases of acute infectious conjunctivitis in LTCF residents are probably viral. Adenovirus has been associated with outbreaks attributed to fomites such as contaminated ophthalmologic diagnostic equipment or medications. A bacterial cause of acute conjunctivitis may be present in less than 40% of cases; most are due to *S. aureus*, *M. catarrhalis*, or *Haemophilus* spp. Epidemics of group A streptococcal conjunctivitis have been reported (48).

### **Secondary Infections**

Most secondary infections of pressure ulcers are due to the polymicrobial flora that colonizes the surrounding perineum. Aerobic flora such as *E. coli*, *Proteus*, *Pseudomonas*, staphylococci, and enterococci may be mixed with anaerobes such as *Peptostreptococcus*, *Bacteroides*, and *C. perfringens* (49–51).

## **Diagnosis and Treatment**

Most SSTIs affect populations outside of LTCFs; the diagnosis and treatment of these conditions do not substantially differ and are discussed elsewhere with a few exceptions below. In general, the McGeer et al., criteria for the diagnosis of SSTI and conjunctivitis emphasize that the definition of infection does not rely on the presence of just one piece of evidence (see Table 1) (18).



However, the diagnosis of scabies in LTCF residents deserves special comment. The diagnosis of scabies infection in LTCF residents can be particularly difficult; symptoms of pruritus, burrows, inflammatory changes in intertriginous areas, and pruritus may be absent. Due to the lack of typical features, the diagnosis may not be suspected for a long-time. Hyperkeratosis or crusted (Norwegian) scabies with abundant organisms can result with long-term infestation. The diagnosis is finally made when more typical rash is found in healthcare workers or visitors (13, 52).

Treatment of scabies in LTCF residents can also be very difficult. While permethrin 5% cream is the treatment of choice, due its lack of central nervous system toxicity, ivermectin has been shown to be effective for severe or refractory cases. Nails should be trimmed and cream should be applied from the neck to toes and left in place for up to 12 h. Secondary cases among other patient contacts should be sought and treated (1, 13).

## **Prevention**

The foremost means of preventing primary skin infection is use of contact isolation where appropriate. Decolonization therapy has been tried in staphylococcal carriers who have recurrent infection; however, it is not clear whether or not infection is prevented (53).

Prevention of secondary infection of pressure ulcers should be directed towards prevention of pressure ulcers themselves through education of healthcare workers, identification of residents at risk, and attention to appropriate use of techniques to reduce pressure, position, and turn patients. Treatment of incontinence is also essential to reduce skin maceration. Finally, use of good nursing, wound care, surgical, and infection control techniques are essential to prevent contamination of wounds by feces and urine and by dirty instruments and hands (1, 49, 50).

Herpes zoster may be transmitted to immunocompromised patients or to healthcare workers who have not had primary infection or vaccination. At minimum, residents with active herpes zoster should be in a private room with contact precautions until all vesicles have crusted. In patients with disseminated disease, some experts recommend airborne isolation (1).

For scabies, washable patient items should be laundered in hot water. The floors should be vacuumed and inanimate surfaces cleaned. Non-washable items can be sealed in plastic for 96 h. Secondary symptomatic cases should be sought and treated. Some experts recommend treating all roommates and persons providing direct care even if they are asymptomatic (1, 13, 54).

## ***Infectious Gastroenteritis and Diarrhea***

### **Epidemiology and Clinical Relevance**

In most surveys of LTCF residents, GI infection is manifested most commonly as gastroenteritis or diarrhea (see also chapter "Infectious Diarrhea"). During one

nation-wide point prevalence survey, 7.0% of LTCF-associated infections were due to gastroenteritis (3). Within the closed environment of the LTCF, spread of enteric pathogens can be facilitated by devices, environmental sources, direct contact with other infected residents or on the hands of personnel, inadequate food preparation, contaminated waters, or following visits by children and pets (55).

Sporadic diarrhea, due to infectious and non-infectious causes, is common in LTCFs. While the exact incidence of gastrointestinal outbreaks in LTCFs is not known, anecdotal reports in numerous facilities suggest that the problem is common (1, 14, 15). It is also known that a significant proportion of reported food-borne illnesses in this country come from LTCFs resulting in high mortality (56). Most deaths due to diarrhea occur in older adults; >50% of all deaths attributed to diarrhea occur in adults aged 74 and older and one-third of these deaths in LTCF residents (2, 14, 15).

### **Etiologic Pathogens**

For most causes of sporadic diarrhea in the LTCF resident, the cause is frequently not identified, there is no specific diagnostic test available for most causes, most treatment is symptomatic, and the course is self-limited. For many cases of diarrhea where an infectious etiology was defined, the cause was only known because sufficient numbers of patients were ill to undertake an outbreak investigation, or a reportable pathogen was isolated. Viral and bacterial etiologies are most common; parasitic infections are reported infrequently.

*C. difficile* is the most readily identified cause of infectious diarrhea in LTCF, in part, because the tests for toxins A and B are readily available and are easily performed, treatment is available and effective, and the presence of the organism has infection control implications (15, 55, 57). Sporadic cases and outbreaks of *C. difficile* have been identified in the LTCF setting. Within 2 weeks of receiving antibiotic therapy, up to one-third of LTCF residents will acquire *C. difficile* (55).

Exposure to *C. difficile* spores in the LTCF environment is common and the introduction of the organism into the resident's GI tract can be facilitated through the contaminated hands of personnel and devices such as feeding tubes and thermometers. Asymptomatic colonization can persist in this population because the host response to *C. difficile*, particularly protective antibody to toxin A, is impaired with increasing age and debility. With the suppressive effect of broad-spectrum antibiotics on the anaerobic flora of the gut, toxin-producing *C. difficile* can emerge and cause diarrhea (55). Newer strains of *C. difficile* that produce higher levels of toxins A and B, and perhaps novel toxins, have led to higher rates of complications among older people including toxic megacolon and death (58).

Most other pathogens are identified only after an outbreak of gastroenteritis is identified and viruses or other bacteria are suspected. Most outbreaks have been due to calciviruses such as norovirus (Norwalk virus), rotaviruses, and adenoviruses. Outbreaks of *Salmonella*, *E. coli* 0157:H7, *S. aureus*, and *C. perfringens* have been associated with improper handling of food. Other uncommon bacterial causes of outbreaks in NH have been due to *Shigella*, *Aeromonas*, *Campylobacter*, and

*Bacillus* species. Rare outbreaks due to parasitic infections such as *Entamoeba histolytica*, *Giardia lamblia*, and *Cryptosporidium parvum* have also been noted (2, 14, 15, 56).

### **Clinical Manifestations and Diagnostic Considerations**

The clinical manifestations of gastroenteritis and diarrhea in older adults are discussed elsewhere (chapter “Infectious Diarrhea”). All LTCF residents with diarrhea will require careful monitoring of fluid status. Adherence to infection control and isolation procedures is also required regardless of etiology, particularly if an outbreak of diarrheal illness is suspected. A diagnostic evaluation would be pursued primarily to determine if more specific treatment options were available, and if increased rates of diarrhea were due to the spread of a single organism. Diarrheal illnesses may be stratified in two ways as gastroenteritis or small bowel infection vs. colitis or large bowel infection (2).

Small bowel infections are manifested by mid-epigastric pain with large-volume watery stools that typically do not contain blood or pus. Viruses and protozoa typically cause small bowel infection. Enterotoxins produced by *Bacillus cereus*, *C. perfringens*, and *S. aureus* also cause nausea and vomiting in addition to watery diarrhea. Most of these pathogens cannot be readily diagnosed by methods available to a LTCF. If the resident is stable with symptoms consistent with small bowel infection, then conservative treatment should be pursued. If symptoms do not remit by 7 days, then stools should be sent for ova and parasites to look for evidence of chronic infection with protozoa (2).

Large bowel infections (colitis) are associated with fever, rectal or lower abdominal cramps, and stools that may contain blood and inflammatory cells. Colitis is caused by *C. difficile*, toxigenic enterohemorrhagic *E. coli*, *Shigella*, *Salmonella*, *Campylobacter*, *Yersinia*, and *Entamoeba histolytica* (2). Stool toxin assays should be done for *C. difficile*, particularly if the patient has had antibiotic treatment within the past 30 days (2). Stool should be sent for culture and susceptibility.

### **Treatment**

All residents should have fluid repletion, treatment of nausea and vomiting, and monitoring and correction of electrolyte imbalances are the primary goals of treatment until results of stool studies are known. For *E. coli* O157:H7, antibiotic treatment is not recommended due to an increased risk of development of hemolytic uremic syndrome (14, 59).

For LTCF residents with moderate to severe illness consistent with toxigenic or invasive diarrhea, antecedent antibiotics should be stopped if possible and empirical treatment for *C. difficile* initiated. Complications such as toxic megacolon may develop rapidly and transfer for more intensive monitoring and surgical consultation should be considered. Residents found to have *C. difficile* in their stool, but

who no longer have diarrhea, should not be treated (55, 58). For invasive diarrheas, treatment should be individualized, based on the organism identified, the resident's clinical condition, and antibiotic susceptibilities. This topic is discussed in more detail elsewhere (14, 15, 60) (see chapter "Infectious Diarrhea").

## Prevention

Fecal-oral spread of infectious gastroenteritis and diarrhea can be prevented by good personal hygiene and hand disinfection on the part of residents, visitors, and healthcare workers. Adherence to appropriate infection control procedures and food preparation guidelines can also prevent spread by contaminated food, water, and other means. Expert consultation should be sought if cases persist despite optimum measures. To eradicate the environmental reservoir of *C. difficile*, disinfection with a sporocidal agent is recommended. Hand washing with soap and water is preferred over the use of alcohol gel. In general, asymptomatic carriers of *C. difficile* do not require routine isolation unless outbreaks and severe disease are occurring despite routine measures (2, 55).

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# Infection Control Programs in Nursing Homes

Lona Mody

## Key Points

- Healthcare delivery has moved from acute care hospitals to multiple settings, including subacute care, long-term care or nursing home (NH), rehabilitation, assisted living, home, and outpatient settings.
- These transitions provide an opportunity for pathogens to be transferred from one setting to another.
- Nursing homes should design their infection control programs based on the population that they serve.
- Infection control programs should address surveillance for infections and antimicrobial resistance, hand hygiene programs, outbreak investigations, immunization programs, antimicrobial utilization program, resident and employee health program as well as infection control in rehabilitation services.
- An Infection control practitioner is crucial for an effective program.

## Background

Healthcare delivery in the United States evolved dramatically over the latter part of twentieth century. In the past, healthcare delivery occurred mainly in acute care facilities. Today, healthcare is delivered in multiple settings, including hospitals, subacute care, long-term care or nursing home (NH), rehabilitation, assisted living, home, and outpatient settings. Efforts to reduce healthcare costs have led to a reduced number of hospitalizations and shorter lengths of stay (with an increase in severity of illness and intensive care unit admissions), along with increased outpatient,

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home care, and NH stays for older adults (1). As a consequence NHs and rehabilitation units are seeing sicker patients who are requiring more intense medical supervision and who are more prone to infections as well as antimicrobial resistance. Infections in NHs increase the mortality and morbidity of residents and generate additional costs for the facilities themselves as well as for hospitals. This chapter highlights infection control implications during care transitions and reviews the infection control issues pertaining to older adults in various healthcare settings with a focus on the NH setting.

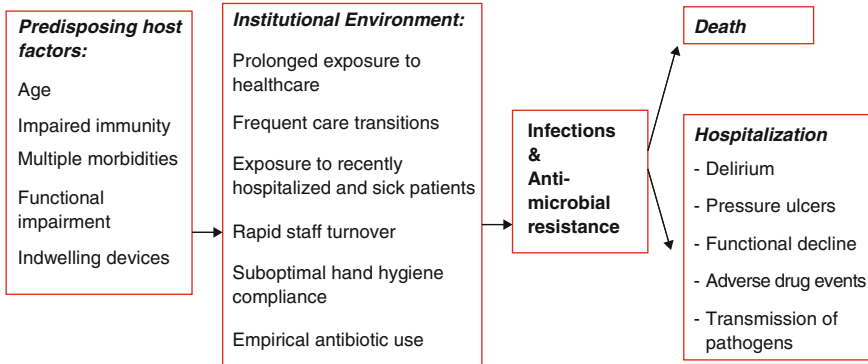
## **Infection Control and Care Transitions**

Transitional healthcare is defined as “a set of actions designed to ensure the coordination and continuity of health care as patients transfer between different locations or different levels of care in the same location” (2). These locations can include acute care hospitals, NHs, skilled nursing facilities, rehabilitation units, home care, outpatient care including same-day surgical units, outpatient infusion rooms, dialysis units, and outpatient primary and other specialty clinics. During care transitions, older adults are susceptible to care fragmentation, which may lead to medical errors and poor quality care. Different financing and contractual agreements with pharmaceutical companies may also impede these transitions. For example, as patients are transferred across settings, each facility has incentives to substitute medications according to their own formulary.

These transitions also provide an opportunity for pathogens to be transferred from one setting to another and the appropriateness of antimicrobial usage, including choice of antibiotics, dosage, and duration. These care transitions also cause practical dilemmas in exercising isolation practices. For example, a patient with methicillin-resistant *Staphylococcus aureus* (MRSA) colonization could be confined to their room during their acute care stay, but he or she may not be isolated in the skilled nursing facility to undergo rehabilitation, again leading to confusion among healthcare workers (HCWs), patients, and families. In summary, infection control issues in older adults vary as they move through various healthcare settings due to the type of care provided, patient characteristics, the unique need for social and personal contact in older adults, and staff and facility resources.

## **Infection Control in Nursing Homes: Challenges**

The nursing home environment can create special challenges for implementing an effective infection control program. First, NHs take care of a vulnerable population of individuals, who are particularly susceptible to infections because of an increased prevalence of chronic diseases, increased severity of illness, medications that affect resistance to infection (such as corticosteroids and frequent antibiotic usage), level



**Fig. 1** Nursing home environment and pathway to infections

of debility, impaired mental status (predisposing to aspiration and pressure ulcers), incontinence and resultant indwelling catheter usage, and the institutional environment in which they live (Fig. 1) (3). Most infections found in these residents are thought to be endogenous in nature and often result from the residents own flora. Nursing home residents also serve as host reservoirs for antimicrobial-resistant pathogens such as MRSA and vancomycin-resistant enterococci (VRE). With reduction in the length of hospital stay, the severity of illness among residents of the subacute care nursing unit has increased with resultant inherent rapid transfers to a hospital and increased polypharmacy. All of these factors combined, have created a vulnerable resident who is highly prone to infections and also to higher disease transmission of resistant pathogens.

In addition, several structural factors impact the implementation of an effective infection control program within a NH. These include suboptimal full-time equivalents for registered nurses, nursing aides and therapists, high staff turnover, changing case mix, limited availability of information systems, and variable availability of laboratory and radiological services. The number of staff per resident varies considerably among facilities (4). The relationship between nursing care intensity and health outcomes for NH patients has been examined for years, and associations between increased nursing hours per patient and improved health outcomes have been reported (5). For example, in a sample of Maryland NHs, registered nurse turnover has been associated with increased risk of infection and a higher risk of hospitalization due to infection (6).

Other factors affecting infection control in NHs include variable staff education, availability and utility of diagnostic specimens, and use of quality improvement tools such as regional databases, quality indicators, and minimum datasets. While the effectiveness of staff education alone is controversial, the value of education as a part of a comprehensive quality control program has long been recognized in all healthcare settings. The importance of staff education is further accentuated by considerable turnover in NH personnel. Nursing aides who are the frontline personnel in recognizing any change in clinical status of NH residents may receive little or no

formal educational training in various infection control issues such as hand hygiene, antimicrobial resistance, early symptoms and signs of common infections, and infection control measures used to reduce infections related to indwelling devices. NHs can overcome these barriers to infection control by scheduling monthly in-services for staff members.

Diagnostic specimens often have limited usefulness in the NH setting for two reasons: (1) they cannot be or are not obtained, and (2) if obtained, the results may not be communicated to the appropriate healthcare provider in a timely fashion, or in the case of radiological investigations, may not be interpreted accurately. The onsite availability of diagnostic or radiology services is lacking in many NHs. In addition, patients may not be able or willing to cooperate in the collection of valid specimens. Diagnostic tests, on the one hand, may thus be infrequently requested, resulting in initiation of therapy without having appropriate clinical information. On the other hand, while urine specimens are more frequently obtained than other types of specimens, the prevalence of bacteriuria in 30-50% of urine specimens means that without an assessment of symptoms, a positive culture has a low predictive value for the appropriate diagnosis of infection. These diagnostic dilemmas can further lead to a delay in initiation of care, inappropriate or unnecessary use of antibiotics, and delayed transfers to acute care for sicker patients.

Despite these challenges, significant progress has been made in adopting infection control guidelines and programs in nursing homes. The next section describes various components of an infection control program in NHs.

## **Infection Control and Prevention: Functions and Elements**

The main functions of an infection control program are the following: (a) to design an individualized surveillance program to identify endemic and epidemic infections in a timely fashion, (b) to develop and to recommend policies and procedures, (c) to intervene directly to prevent infections, and (d) to educate and to train HCWs, patients, and non-medical caregivers (1). Thus, an effective infection control program typically includes a method of surveillance for infections and antimicrobial-resistant pathogens, an outbreak control plan for epidemics, isolation and standard precautions, hand hygiene, staff education, an employee health program, a resident health program, policy formation, and periodic review with audits, and a policy to communicate reportable diseases to public health authorities (Fig. 2).

### ***Surveillance***

Infection surveillance in NHs involves collection of data on NH-acquired infections. Surveillance is defined as “ongoing, systematic collection, analysis, and interpretation of health data essential to the planning, implementation, and evaluation of public

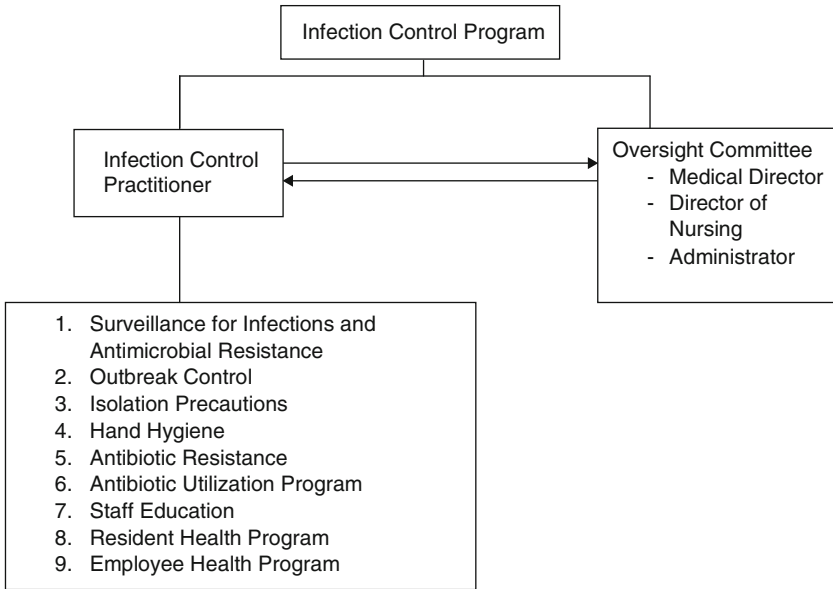


Fig. 2 Components of infection control program in long-term care facilities

health practice, closely integrated with timely dissemination of these data to those who need to know” (7). Surveillance can be limited to a particular objective or may be facility-wide. Surveillance is often based on individual patient risk factors, focused on a unit, or based on a particular pathogen or infection type.

Surveillance can be either passive or active. In passive surveillance, also known as routine surveillance, an infection control professional uses data collected for routine patient care. While less costly in terms of resources, passive surveillance is inherently biased. It may also underestimate the magnitude of the outcomes measured and delay detection of outbreaks. The feasibility of passive surveillance has been demonstrated and has led to continuing education opportunities. Active surveillance, unlike passive surveillance, utilizes multiple data sources to detect infections and antimicrobial resistance early. It requires routine infection control practitioner (ICP) rounds to detect infections early and may involve patient screening for resistant pathogens. Active surveillance for antimicrobial-resistant pathogens in acute care has created significant debate in recent years, although data in NHs are lacking.

For surveillance to be conducted correctly, objective, valid definitions of infections are crucial. Hospital surveillance definitions are based on the National Nosocomial Infection Surveillance (NNIS) criteria, which depend rather extensively on laboratory investigations. Radiology and microbiology data are less available, and, if available, are delayed; therefore, these criteria may not be applicable in NH settings. Modified NH-specific criteria were developed by a Canadian

consensus conference, which took into account the unique limitations of the NH setting (8). They have been used widely, although not uniformly (4).

Besides using valid surveillance definitions, a facility must have clear goals and aims for setting up a surveillance program. These goals, as with other elements of an infection control program, have to be reviewed periodically to reflect changes in the facility's population, pathogens of interest, and changing antimicrobial resistance patterns. Plans to analyze the data and use of these data to design and implement proven preventive measures must also be made in advance.

The analysis and reporting of infection rates in NHs are typically conducted monthly, quarterly, and annually to detect trends. If the length of stay at a NH is typically long, and each resident is at risk for a prolonged duration, an analysis of absolute numbers of infections can be misleading. Infection rates (preferably reported as infections/1,000 resident-days) can then be calculated by using resident-days or average resident census for the surveillance period as the denominator.

These data can be used to establish endemic baseline rates and to recognize variations from the baseline that could represent an outbreak. Critical to the success of any surveillance program is the feedback of these rates to the nursing staff, physicians, and appropriate quality control and review committees. This information should eventually lead to specific, targeted infection control initiatives and follow-up surveillance to evaluate the success of the changes.

Furthermore, surveillance data can be combined at a regional or a national level, and individual facility rates can be compared with an aggregate of other facilities using visual and simplified statistical methods (9). The success in the reduction of nosocomial infection rates in acute care hospitals that participate in an NNIS system has been demonstrated. While one study has demonstrated the feasibility of using interfacility comparisons among 17 NHs, similar NNIS-like system needs to be studied further at other sites (9).

## ***Outbreak Investigations and Control***

An illness in a community or region is considered an outbreak when it clearly exceeds the normal rate of expectancy. The existence of an outbreak is always relative to the number of cases that are expected to occur in a specific population in a specific time period. The main objectives of an outbreak investigation are control and elimination of the source, prevention of new cases, prevention of future outbreaks, research to gain additional knowledge about the infectious agent and its mode of transmission, program evaluation and strategies for improvement, and epidemiological training to conduct outbreak investigations.

A NH ICP should know the following: (1) appropriate data collection methods, (2) how to interpret the data using simple epidemiologic measures, (3) effective study designs in order to conduct an effective and efficient outbreak investigation, and (4) effective and appropriate infection control measures. While local health departments are available for counsel, it may also be beneficial for the ICP to have access to a hospital epidemiologist for consultation.

## ***Antibiotic Resistance***

Infection and colonization with antimicrobial-resistant pathogens are important concerns in NHs and develop primarily due to widespread use of empirical antibiotics, functional impairment, the use of indwelling devices, mediocre adherence to hand hygiene programs among HCWs, and cross-transmission during group activities. A NH can reduce infections and colonization with resistant pathogens by emphasizing hand hygiene compliance, by developing an antimicrobial utilization program, by encouraging evidence-based clinical evaluation and management of infections, and by ensuring that the facility has a well-established individualized infection control program. Guidelines to control MRSA and VRE have been published by Society for Healthcare Epidemiology of America (SHEA) and provide a good base for developing facility-specific policies (10).

## ***Isolation Precautions***

The Centers for Disease Control and Prevention's Healthcare Infection Control and Prevention Advisory Committee (HICPAC) has proposed a two-tiered structure for isolation precautions: In the first tier, HICPAC proposes use of "Standard Precautions," which have been designed for the care of all patients in all healthcare settings, regardless of their diagnosis, infectious or otherwise; in the second tier are "Transmission-based Precautions," which have been designed for the care of patients suspected of or known to be infected with epidemiologically important pathogens that have been acquired by physical contact or airborne or droplet transmission (11).

Standard precautions apply to blood, all body fluids, secretions and excretions regardless of whether they contain visible blood, non-intact skin, and/or mucous membrane material. Designed to reduce the risk of transmission of pathogens, both from apparent and ambiguous sources of infection, these precautions include hand hygiene compliance, glove use, masks, eye protection, and gowns, as well as avoiding injuries from sharps. Transmission-based precautions are intended for use with patients who may be infected with highly transmissible or epidemiologically significant pathogens. These include airborne precautions (e.g., for tuberculosis), droplet precautions (e.g., for influenza), and contact precautions (e.g., for *Clostridium difficile*). Decisions regarding NH resident placement or isolation should be made on a case-by-case basis by balancing the risk of transmission, by infection risk to the other residents as well as by the psychological consequences of isolating colonized residents (11).

There has been some debate, in acute care hospitals, on the role of active surveillance cultures and their impact on isolation policies. The SHEA guideline for preventing nosocomial transmission of multi-drug resistant organisms advocates for aggressive active surveillance cultures (12), whereas the recent draft of HICPAC guidelines call for individual facilities to assess their own needs and conduct

surveillance cultures as necessary (13). These guidelines refer to studies from acute care hospitals serving a sicker, shorter stay population. Facilities should evaluate these guidelines and individualize their plan to obtain active surveillance cultures based on the population they serve, to obtain baseline rates of MRSA and VRE, and any recent outbreaks.

### ***Antimicrobial Utilization Program***

Several strategies have been proposed or studied to reduce inappropriate antimicrobial practices in NHs (14). These include antimicrobial utilization review by the infection control committee to monitor antibiotics prescribed in the NH, the development and promotion of programs to optimize judicious antibiotic use, and as-needed audit to assess antibiotic appropriateness, prevalence of antibiotic resistance, and antibiotic related adverse events. A recent study in multiple NHs in the United States and Canada evaluated the effectiveness of a more proactive approach that advocated using clinical algorithms targeted to physicians and nurses and implementing a multi-component program of education, written material, real-time reminders, and outreach visits to reduce urinary tract infections. The study showed a 31% reduction in antimicrobial use for urinary indications (15). Nursing homes can use realistic interventions such as an antibiotic guide, developed with the assistance of the facility pharmacist listing common infections, recommended empirical antibiotics, and the dosage, frequency and duration of treatment (16). Teaching sessions including national guidelines, facility resistance data and physician feedback, and distribution of booklets detailing institutional guidelines on optimal management on various NH infections can also be used (17).

### ***Hand Hygiene Compliance***

Since the observations of Holmes, Semmelweis, and others more than 100 years ago, contamination of the hands of HCWs has been recognized to play a role in the transmission of pathogenic bacteria to patients. Hand antisepsis remains the most effective and least expensive measure to prevent transmission of nosocomial infections. However, compliance with hand-washing recommendations among HCW averages only 30–50% and only improves modestly following educational interventions (18). Reasons frequently reported for poor compliance with hand-hygiene measures by HCWs include skin irritation from frequent washing, too little time to cleanse hands due to a high workload, and simply forgetting.

The use of waterless, alcohol-based handrubs as an adjunct to washing hands with soap and water has become a routine practice by HCWs in many acute care facilities (19, 20). Introduction of alcohol handrub has been shown to significantly improve hand-hygiene compliance among HCWs in acute care hospitals and has

also been shown to decrease overall nosocomial infection rates and transmission of MRSA infections.

Alcohol handrub has also been shown to enhance compliance with hand hygiene in the NH setting and should be used to complement educational initiatives (18). While introducing the alcohol handrub in healthcare settings is a prudent, cost-effective measure, several issues need to be considered. Alcohol handrub should not be used if hands are visibly soiled, in which case hand hygiene with antimicrobial soap and water is recommended. Facilities should be aware that alcohols are flammable. Facilities have reported difficulties in implementing the current hand-hygiene guidelines and the use of alcohol-based handrubs due to the fire-safety concerns. Existing national fire codes permit use of alcohol-based handrub dispensers in patient rooms, but they cannot be used in egress or exit corridors. Since the state and local fire codes may differ from national codes, facilities should work with their local fire marshals to insure that the installation of alcohol-based handrub containers is consistent with local fire codes. In addition, alcohol handrub may be ineffective in eliminating *C. difficile* spores. As a result, antimicrobial soap and water is recommended when taking care of patients with *C. difficile* (11).

### ***Staff Education***

Ongoing staff education is important in healthcare settings due to the plethora of literature published every year, advancements in technology, and regulatory demands. The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) expects new employee orientation to include the facility's infection control program and the employee's individual responsibility is to prevent infections. In addition, for any employee expected to come into contact with potentially infectious agents, the Occupational Safety and Health Administration (OSHA) require training for blood-borne pathogens and tuberculosis.

The infection control practitioner plays a vital role in meeting these requirements and in educating NH personnel on various infection control measures, particularly in view of rapid staff turnover. Informal education during infection control and quality improvement meetings as well as during infection control walking rounds should be complemented with in-service education on various topics. These topics include the following: hand-hygiene compliance, antimicrobial usage and antimicrobial resistance, appropriate and early diagnosis of infections, infection control and prevention measures to prevent these infections, and isolation precautions and policies.

### ***Resident Health Program***

The resident health program should focus on immunizations, tuberculin testing, and infection control policies to prevent specific infections such as skin care, oral hygiene, prevention of aspiration, and catheter care to prevent urinary tract infections.



Adults age 65 and older should receive pneumococcal vaccination at least once, influenza vaccination every year, and a tetanus booster every 10 years. Both influenza and pneumococcal vaccination rates are now monitored and publicly reported by the Centers for Medicare and Medicaid Services (CMS).

### ***Employee Health Program***

The employee health program mainly concerns employees with potentially communicable diseases, policies for sick leave, immunizations, and OSHA regulations to protect them from blood-borne pathogens. It is a requirement that NHs bar employees with known communicable diseases or infected skin lesions from providing direct contact with the residents; employees with infected skin lesions or infectious diarrhea should be prevented from having direct contact with residents' food. Moreover, when hiring new employees, an initial medical history must be obtained along with a physical examination and screening for tuberculosis. Infection control education must also be provided to staff members.

Infection control policies and measures in NHs must be in place to address post-exposure prophylaxis for infections such as human immunodeficiency virus and hepatitis B virus. Varicella vaccine should be given to employees not immune to the virus. Employees are expected to be up-to-date with their tetanus boosters and to receive influenza vaccinations every year. Not only is the vaccine effective in preventing influenza and reducing absenteeism in HCWs, but it has also been associated with a decrease in influenza mortality in patients (21). Annual influenza vaccination campaigns play a central role in deterring and preventing nosocomial transmission of the influenza virus and should be promoted by the ICP and NH leadership.

### ***Rehabilitation Services***

Nursing homes are increasingly responsible for post-acute care rehabilitation, including physical therapy (PT), occupational therapy (OT), and wound care with or without hydrotherapy. These therapists, like other clinical staff such as nurses and nurses' aides, provide many opportunities for the transmission of pathogens. In a NH, PT and OT services can be provided either at the bedside or in a central therapy unit. For bedside therapy, therapists move between rooms and units and do not routinely wear gloves and gowns. For care at a central therapy unit, residents are transported to an open unit where hand-washing sinks may not be readily available. While these therapists have not been implicated in any major outbreaks, hydrotherapy for wounds has been shown to facilitate outbreaks with resistant pathogens (22).

A detailed infection control program for rehabilitation services should be prepared and should focus on facility design to promote hand-hygiene compliance, including

convenient and easy access to sinks and the use of alcohol handrubs. Patients who are infectious should not be treated at the central facility. Facilities providing hydrotherapy should consider providing the service in a separate room with a separate resident entrance.

### ***Infection Control Practitioner***

An ICP, usually a staff nurse, is assigned the responsibility of directing infection control activities in a NH. The ICP is responsible for implementing, monitoring, and evaluating the infection control program. Due to financial constraints, an ICP will also usually function as an assistant director of nursing or will be involved in staff recruitment and education. Whether or not a full-time ICP is needed, depends on the number of beds, the acuity level of residents, and the level of care provided at the facility. Nonetheless, for an infection control program to succeed, the ICP should be guaranteed sufficient time and resources to carry out infection control activities. A basic background in infectious disease, microbiology, geriatrics, and educational methods is advisable. The ICP should also be familiar with the federal, state, and local regulations regarding infection control. An alliance with and access to an infectious disease epidemiologist should be encouraged. Such collaborations could also provide assistance with outbreak investigations, emergency preparedness in the event of bioterrorism and vaccine shortages, and the use of microbiologic and molecular methods for infection control.

### ***Oversight Committee***

The Federal Nursing Home Reform Act from the Omnibus Budget Reconciliation Act of 1987 mandated the formation of a formal infection control committee to evaluate infection rates, implement infection control programs, and review policies and procedures. However, at the federal level, this mandate has been dropped by OBRA, although some states may still require an oversight committee. A small subcommittee or a working group comprised of a physician/medical director, an administrator, and an ICP should evaluate the NH infection rates on a regular basis and present the data at quality control meetings, review policies and any research in the area, and make decisions to implement infection control changes. This subcommittee can review and analyze the surveillance data, they can assure that these data are presented to the nursing and physician staff, and they can approve targeted recommendations to reduce such infections. Records pertaining to these activities and infection data should be kept and filed for future reference.

Principles guiding infection control practices also provide a model for enhancing quality of care and patient safety for other non-infectious adverse outcomes such as falls, delirium, inappropriate medication usage, and adverse drug events.

## Infection Control in Home Care Settings

With a move towards reduced hospital stay, home healthcare delivery remains the fastest growing segment in healthcare. Established in the 1880s, the home care industry grew from 1,100 home healthcare organizations by 1963 to over 20,000 in 2004 (23). Per the 2000 Home and Hospice Care Survey, about 7.2 million individuals received home healthcare (5 million or 69% being age 65 years and older). This represents an increase of nearly 90% in 15 years. Home healthcare agencies, home care aide organizations, and hospices are collectively known as “home healthcare organizations.” Durable medical equipment and supply companies, while not included under the traditional “home healthcare” umbrella, are ancillary to home healthcare and provide products ranging from respirators and sleep apnea machines to walkers, catheters, and wound care supplies.

These home healthcare organizations provide care for elderly adults who frequently have multiple medical problems, including diabetes mellitus, congestive heart failure, cancer, chronic obstructive pulmonary disease, and chronic wounds. Coupled with the use of indwelling devices, such as urinary catheters, intravascular catheters, and feeding tubes, their infection risk increases tremendously. Data on the epidemiology of infections in this group are limited, albeit several outbreaks of bloodstream infections have been documented (24, 25).

While attempts have been made to standardize surveillance definitions, several challenges remain (26). These challenges include the fact that few dedicated infection control personnel are employed by home healthcare agencies, the role of informal care-giving in the spread of infections and adherence to infection control recommendations, and the paucity of data to understand the epidemiology of infections among patients receiving home healthcare.

## Resources for Infection Control Practitioners

1. Society for Healthcare Epidemiology of America (SHEA) and the Association for Professionals in Infection Control (APIC) both have long-term care committees that publish and approve NH infection guidelines and publish periodic position papers related to pertinent infection control issues. Their websites have several educational resources for staff education and in-services. In addition, APIC also publishes a quarterly long-term care newsletter.
2. Local APIC chapters provide a network for infection control practitioners to socialize, discuss infection control challenges and practical solutions to overcome them, and provide access to educational resources and services. Infection control practitioners should become members of APIC at both the local and national level to remain up-to-date with practice guidelines, position statements, information technology resources, and changes in policies and regulations.
3. *Hospital Epidemiology and Infection Control* (3rd ed.); C. Glen Mayhall, ed.: Philadelphia, PA: Lippincott Williams & Wilkins, 2004.

#### 4. Selected Internet Websites:

- (a) Centers for Disease Control and Prevention (CDC): <http://www.cdc.gov>
- (b) Society for Healthcare Epidemiology of America (SHEA): <http://www.shea-online.org/>
- (c) Association for Professionals in Infection Control (APIC): <http://www.apic.org>
- (d) Occupational Health and Safety Administration (OSHA): <http://www.osha.gov>
- (e) Joint Commission on Accreditation of Healthcare Organizations-Infection Control Initiatives: <http://www.jcaho.org/accredited+organizations/patient+safety/infection+control/ic+index.htm>

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## Suggested Reading

See under Resources for Infection Control Practitioners

# Infections in Diabetics

Shobita Rajagopalan

## Key Points

- Diabetes mellitus occurs in approximately 18% of persons between the ages of 65 and 75 and in up to 40% of persons over age 80 years.
- Elevated serum glucose levels associated with diabetes mellitus alter host immune responses, resulting in predisposition to infections.
- The cumulative effect of age-related immune senescence, superimposed on this enhanced risk of infections in diabetics, can, in elderly diabetics, lead to serious and life-threatening infectious processes.
- Because infection associated with aging can present in a subtle manner, prompt recognition of infection and treatment with appropriate empirical broad-spectrum antimicrobial agents in conjunction with surgical intervention may be needed to eradicate such infections.
- Common sites of infection associated with diabetes mellitus include the respiratory tract, the gastrointestinal tract, the urinary tract, as well as the skin, soft tissue, and bony structures particularly of the feet.

## Background and Epidemiology

Diabetes mellitus (DM) is a common chronic disease that afflicts 7–8% of the overall adult population of the United States (1, 2). DM occurs in an estimated 18% of persons between the ages of 65 and 75 years and in as many as 40% of persons over 80 years of age. Approximately 23% of persons aged 65–70 years have glucose intolerance, and nearly 50% of elderly diabetics are undiagnosed (3, 4). The vast majority of these individuals (90–95%) belong to the type II category and the rest

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belong to type I. Some investigators have linked persistently elevated blood glucose levels in individuals with DM to the subsequent development of infection and/or to the inability to control established infection (5). Conversely infections by themselves can destabilize diabetic control; marked hyperglycemia and/or ketoacidosis can, in turn, make the control of infection increasingly challenging.

Optimizing glycemic control can help prevent common and life-threatening infections associated with DM. In addition, the enhanced susceptibility to infection in diabetics has also been attributed to defects in both cell-mediated immunity (CMI) and humoral immunity (6). Furthermore, immune senescence, which predominantly affects CMI, can result in a cumulative risk for intracellular bacterial, mycobacterial, fungal, and viral infections (7, 8). Clinical experience has demonstrated that elderly diabetics are especially susceptible to infection. Although infections in elderly individuals with diabetes may seem to be no different from those encountered by their younger counterparts, the combination of immune system alteration that can potentially result from DM and aging can presumably lead to serious and life-threatening complications of infection. Moreover, because a significant number of infections in elderly individuals are known to present in an atypical manner, prompt recognition and treatment with appropriate empirical broad-spectrum antimicrobial agents and surgical intervention, as indicated, is often key to the successful eradication of such infections (5). Although minimal data exist regarding the pathophysiologic basis of the enhanced susceptibility to infection in elderly diabetics, many studies strongly indicate an overrepresentation of specific infections in this subset of the elderly (9, 10).

This chapter will highlight important immune defects that result in an increased susceptibility to infections in elderly diabetics and review unique clinical aspects of specific serious infections predominantly encountered in this particular population.

## **Aging, DM, and Immunity**

Published data evaluating age-related changes in immune function has largely pointed toward the CMI system. Although the total number of T lymphocytes does not vary with age, functional changes in various subsets have been demonstrated (8, 11–13). Aging T cells tend to secrete less interleukin (IL)-2 (which stimulates proliferation and differentiation of other T-cell clones); this functional effect, however, does not consistently affect all T-cell subsets. The proportion of naive T cells (i.e., T cells that respond to new antigens) decreases as thymic involution occurs with a reduction in the production of thymic hormones. As a result, most T cells in elderly persons have already had prior antigenic exposure (i.e., they are memory T cells) thus explaining why elderly individuals respond more effectively to antigens previously encountered than to new antigens (11, 12). This phenomenon may also explain the enhanced tendency for reactivation of infection with intracellular pathogens such as *Mycobacterium tuberculosis* and varicella-zoster virus (14). During aging, humoral immunity is relatively unaffected with the exception of

B-cell functions that are mediated with the cooperation of T-helper cells. Overall, immunoglobulin levels remain constant with age, but their proportions may change with an increase in IgG or IgM levels and various changes in IgA levels (15, 16). These changes may explain the less than optimal response to certain immunizations (e.g., pneumococcal and influenza vaccinations) (17, 18).

In patients with DM, abnormalities in polymorphonuclear neutrophils (PMNs), monocytes, and lymphocytes related to adherence, chemotaxis, opsonization, ingestion of bacteria, oxidative burst, and intracellular killing have been described (3, 19–21). The significantly negative correlation between glycated hemoglobin levels and neutrophil bactericidal activity has been attributed partly to the degree and to the duration of hyperglycemia and may be reversed with optimal glycemic control (19). Hyperglycemia, or the presence of advanced glycation end products, is believed to lead to a state of low-level, persistent activation in PMNs. This hyper-excited state leads to spontaneous activation of the oxidative burst and to the release of neutrophil granule components that may, in turn, lead to a “burned-out” or tolerant PMN which responds less vigorously when stimulated by an infectious pathogen, and thus initiates pathologic processes leading to vascular injury. Resting levels of cytokines (e.g., tumor necrosis factor- $\alpha$ , IL-6, and IL-8) are elevated in individuals with DM, but on stimulation, the cells produce less IL-1 and IL-6 than do similar cells in control subjects. In addition, abnormalities in monocyte and macrophage chemotaxis and phagocytosis have been reported (3). Adaptive cellular immunity does appear to be affected, however, with decreased lymphocyte proliferative response to stimulants (e.g., phytohemagglutinin) and certain pathogens (e.g., *Staphylococcus aureus*) but normal response to others (e.g., *Candida albicans*) (22). Abnormal delayed-type hypersensitivity responses have also been described in individuals with DM. Humoral immunity appears to be normal, with normal levels of immunoglobulins and normal response to vaccinations (3). However, diabetics have also been shown to have deficiency in the fourth component of complement and decreased opsonization of microorganisms such as *Candida albicans* (16). (Table 1 shows immune-system defects commonly seen in aging versus DM.)

**Table 1** Effects of aging and diabetes mellitus on the immune system

Aging	Diabetes mellitus
Minimal changes in functions of polymorphonuclear leukocytes except possible decreased phagocytic capacity	Polymorphonuclear leukocytes, monocytes and lymphocytes demonstrate a decrease in adherence, chemotaxis, and intracellular killing
Functional change in T-cell subsets, with a decrease in IL-2 secretion	Cell-mediated immune responses are reduced, with a decrease in proliferative response to phytohemagglutinin and <i>Staphylococcus aureus</i>
Naive T cells have decreased ability to respond to new antigens	Abnormal delayed-type hypersensitivity responses
Humoral immunity mildly affected	Humoral immunity remains relatively intact
Overall immunoglobulin (Ig) levels remain constant; IgM, IgG, and IgG subsets vary with aging	Little to no changes in immunoglobulin levels; deficiency in fourth component of complement

Note. Data are adapted from (5–17)



## Unique Aspects of Infection in Elderly Diabetics

Although most elderly individuals demonstrate clinical manifestations consistent with infection (e.g., fever, chills, and elevated white blood count), a significant number of geriatric patients present with atypical features that may be less apparent or absent (e.g., weakness, malaise, and/or confusion) and that may be the only manifestation of the illness (21). Clinicians must be cognizant of factors that may potentially influence presentation of infections in elderly individuals such as underreporting of illnesses, because of cultural and educational background, depression, cognitive impairment, or denial; changing patterns of illness (e.g., susceptibility to infections caused by gram-negative bacilli, mycobacteria, and viruses); and variable clinical responses, as mentioned. Common infections in elderly individuals with diabetes are similar to those encountered in younger individuals with DM. Particular infections of importance in elderly diabetics will be described below.

### Specific Infections (See Tables 2 and 3)

#### *Respiratory Tract*

##### **Rhinocerebral Mucormycosis**

More than 75% of the reported cases of the fungal disease rhinocerebral mucormycosis (also called zygomycosis) occur in diabetics; generally these diabetics are in states of poor metabolic control and ketoacidosis (see also the chapter “Fungal Infections”). Paranasal sinuses and the palate may be initially involved with this infection, with later spread of this disease to the retroorbital area, the cavernous sinus, and intracranial sites, including the frontal lobes. A variety of fungal organisms may be associated with this condition, the most common being in the family Mucoraceae, including *Rhizopus*, *Absidia*, and *Mucor* species. Ketoacidosis is thought to be the most likely predisposing factor, although it is present in only ~50% of the patients with diabetes who have this infection. Various hypotheses have attempted to explain this predilection and include the enhanced availability of iron for the pathogen at lower pH levels and pulmonary macrophages of individuals with DM showing diminished ability to prevent germination of *Rhizopus* species (23). The pathogenesis of the diseases probably begins with inhalation of the fungus into the paranasal sinuses. Local spread of the infection may result in osteomyelitis, proptosis, ophthalmoplegia, blindness, cavernous sinus thrombosis, meningoencephalitis, and brain abscesses. Fungal invasion of blood vessels causes thrombosis and often results in tissue infarctions. Diagnosis is generally made by a biopsy of the marginal areas of the necrotic black eschars, which are characteristically

**Table 2** Infections in elderly patients with diabetes mellitus

Site of infection	Common infections	Serious and predominant <sup>a</sup> infections
Respiratory tract	Pneumonia <sup>b</sup> , tuberculosis <sup>b</sup>	Rhinocerebral mucormycosis <sup>b</sup> , malignant otitis externa <sup>b</sup>
Gastrointestinal tract	Oral and esophageal candidiasis <sup>b</sup>	Emphysematous cholecystitis <sup>b</sup>
Urinary tract	Bacteriuria and cystitis <sup>b</sup> (women), pyelonephritis <sup>b</sup> , renal/perinephric abscess <sup>b</sup> , papillary necrosis <sup>b</sup>	Emphysematous cystitis <sup>b</sup> , emphysematous pyelitis, emphysematous pyelonephritis <sup>b</sup>
Skin, soft tissue, and bone	Superficial non-necrotizing infections <sup>b</sup>	Superficial and deep necrotizing infections <sup>b</sup>

*Note.* Data are modified from (1)

<sup>a</sup>Predominant infections: >50% of cases are associated with diabetes mellitus

<sup>b</sup>Specific infections reviewed in this chapter

**Table 3** Treatment of serious infections in elderly patients with diabetes mellitus

Site of infection, infection(s)	Treatment(s)
<b>Respiratory tract</b>	
Rhinocerebral mucormycosis	Surgical debridement and amphotericin B therapy (lipid formulations may be used); the efficacy of new antifungal agents, including the triazole posaconazole and the echinocandin caspofungin, needs further evaluation; the efficacy of hyperbaric oxygen and granulocyte colony-stimulating factor needs further evaluation
Malignant otitis externa	Antipseudomonal penicillin, cephalosporin, or fluoroquinolone with or without an aminoglycoside
<b>Gastrointestinal tract</b>	
Emphysematous cholecystitis	Antimicrobial therapy with fluoroquinolones, third- or fourth-generation cephalosporins with or without antianaerobic agents (clindamycin or metronidazole or $\beta$ lactam- $\beta$ lactamase inhibitor combination agents)
<b>Urinary tract</b>	
Emphysematous cystitis, emphysematous pyelitis, emphysematous pyelonephritis	Antimicrobial therapy with fluoroquinolones, third- or fourth-generation cephalosporins with or without antianaerobic agents (clindamycin or metronidazole or $\beta$ lactam- $\beta$ lactamase inhibitor combination agents)
<b>Skin, soft tissue, and bone</b>	
Superficial and deep necrotizing infections	Surgical debridement and broad-spectrum antimicrobial therapy to cover mixed infection with gram-positive, gram-negative, and anaerobic pathogens (e.g., therapy with penicillin and clindamycin); the efficacy of hyperbaric oxygen for necrotizing skin and soft-tissue infections needs further evaluation

seen in this disease entity. Potassium hydroxide (KOH) or stained tissue preparations will show thick hyphae, which have rare septations and with right-angle branching.

Aggressive surgical extirpation of infected bone and soft tissue is required. Repeated debridement is often necessary. Intravenous (IV) amphotericin B at 1.0–1.5 mg/kg/day (or liposomal amphotericin B at 5.0 mg/kg/day) may be given

up to total doses of 2.0–4.0 g (24). The role of the newer azole antifungal agents (e.g., posaconazole and ravuconazole), echinocandins (e.g., caspofungin and micafungin), or flucytosine in treating this infection needs further investigation. An increase in the trends of zygomycoses has been reported in immunocompromised patients who received voriconazole for the treatment of infections due to *Aspergillus* species (25). Greenberg et al., studied 23 cases of zygomycosis in patients who were intolerant of or refractory to standard therapies; posaconazole therapy was found to be successful in 70% of cases (26). However, many patients in this study also underwent surgical therapy, complicating accurate assessment of the role of posaconazole therapy in the favorable outcome. Another trial evaluating the safety and efficacy of posaconazole treatment in elderly patients with refractory zygomycoses, suggested that posaconazole may provide a treatment option for elderly patients with invasive fungal infections (27). Untreated, the disease is universally fatal, but aggressive surgery and long-term therapy with amphotericin B can lead to a mortality rate as low as 16.7% (28–30). The usefulness of other therapies such as hyperbaric oxygen therapy and therapy with granulocyte colony-stimulating factor remains to be determined (30).

### **Invasive External Otitis**

In contrast to the more common external otitis often seen in children (“swimmer’s ear”), invasive (or necrotizing) external otitis in older adults is a much more aggressive infection. Approximately 90% of patients with this disease are diabetics, frequently in poor metabolic control (see also the chapter “Otitis Externa, Otitis Media, and Sinusitis”). Except for unusual cases caused by other organisms such as *Aspergillus* and *Klebsiella pneumoniae*, virtually all cases are associated with *Pseudomonas aeruginosa*; the presence of granulation tissue at the junction of the bony and cartilaginous portions of the external canal is a characteristic clinical finding (31, 32). Local spread along this cleft or junction may result in osteomyelitis of the temporomandibular joint, parotitis, and mastoiditis. Deeper invasion may result in cranial nerve IX–XII palsies, septic sigmoid sinus thrombophlebitis, and meningoencephalitis. Involvement of cranial nerve VII resulting in facial palsy, due to inflammation of the stylomastoid canal exit site, is fairly common (30–40% of cases) and may not necessarily imply a dire prognosis. Computed tomographic (CT) and magnetic resonance imaging (MRI) scans have dramatically improved the clinician’s ability to determine the extent of involvement of bony and intracranial structure in this disease process.

Management includes early and aggressive debridement of the external auditory canal. Bony sites of involvement may also need debridement and administration of appropriate antimicrobial therapy. Since *P. aeruginosa* is almost always the pathogen involved, therapy frequently consists of parenteral, high-dose antipseudomonal  $\beta$ -lactam agent, such as piperacillin, ceftazidime, cefepime, or aztreonam, in combination with an aminoglycoside for synergistic antimicrobial activity. Extreme caution must be exercised when giving aminoglycosides to elderly persons and

to diabetics, especially those with preexistent renal insufficiency. Since the aminoglycosides under these conditions are given primarily for synergy, maximum doses may not be necessary, and the drug may be given once or twice daily to decrease nephrotoxicity (Published reports regarding antimicrobial treatment of malignant external otitis) suggest that oral (PO) ciprofloxacin may be effective in selective cases (33). Parenteral therapy with  $\beta$ -lactams will generally require a total minimum duration of 4 weeks, but longer therapy (i.e., 3 months) has been suggested for oral ciprofloxacin. Gallium scans and erythrocyte sedimentation rates may be useful to document response and ensure adequate duration of therapy.

## ***Gastrointestinal Tract***

### **Emphysematous Cholecystitis**

Approximately 35% of the reported cases of the highly virulent emphysematous cholecystitis have occurred in diabetics (34). Compared with the usual form of cholecystitis, this entity has shown a preponderance of males (70%), a high incidence of gallbladder wall gangrene (74%) and perforation (21%), and high mortality (15–25%). Absence of concomitant gallstones is seen in one-half of these cases. Infection is frequently polymicrobial with gram-negative bacilli such as *Escherichia coli* and *Klebsiella* spp., as well as *Clostridium perfringens* among the most commonly isolated microorganisms. A high index of suspicion, followed by prompt and aggressive surgery and appropriate antimicrobial therapy, may help decrease the morbidity and mortality of this disease entity.

## ***Urinary Tract***

### **Emphysematous Pyelonephritis**

Emphysematous pyelonephritis generally presents as a fulminant, life-threatening illness. Seventy percent to 90% of the patients with of emphysematous pyelonephritis are diabetic, and the infection is almost always unilateral, affecting the left kidney more often than the right one (35). There is characteristic mottled gas found in and around the kidney, often detectable with plain upright abdominal radiograph, and clearly demonstrated by CT scan. Associated urinary tract obstruction is seen in 40% of diabetic patients and in virtually all of the non-diabetic patients. *E. coli* is the culprit pathogen in 70% of the cases. Pathologically, necrotizing pyelonephritis, cortical abscesses, and sometimes papillary necrosis are present. Clinically, the patient presents with fever, chills, flank pain, confusion, and generalized sepsis. Although a few cases have responded to medical therapy alone, higher survival rates have been associated with combined antibiotic therapy plus nephrectomy. Because aging and DM (diabetic nephropathy) are associated with renal insufficiency, careful

assessment of kidney function is also essential in the management of emphysematous pyelonephritis and all forms of urinary tract infection in elderly diabetics.

### **Emphysematous Cystitis**

*E. coli* and other members of the Enterobacteriaceae family are generally responsible for emphysematous cystitis, which is generally more benign than emphysematous pyelonephritis. At least 80% of the reported cases of emphysematous cystitis occur in diabetics (36), who may present with pneumaturia; gas in the urinary bladder wall may be seen on plain abdominal X-ray or by abdominal CT scan. The disease is generally responsive to antimicrobial therapy.

### **Perinephric Abscesses**

Perinephric abscess should be suspected in patients with urinary tract infection and fever of at least 5-day duration that is unresponsive to appropriate antimicrobial therapy (37). Approximately 35% of the cases have associated DM, and about half of the patients will present with abdominal or flank mass.

The diagnosis of perinephric abscess is generally established by ultrasonography or CT or MRI scan. Surgical drainage, done by either open surgery or percutaneous catheter placement, in combination with about 4 weeks of antimicrobial therapy, are generally effective in the management of this disease. Ureteral obstruction needs to be excluded. *E. coli* is the most common isolate, and ascending infection is the usual route of spread.

## ***Skin and Soft-Tissue Infections***

### **Superficial Non-necrotizing Infections**

Increased nasal carriage of *S. aureus* has been reported in insulin-injecting diabetics (38). However, increased propensity of diabetics to staphylococcal furunculosis and carbuncles has not been conclusively proven. Erythrasma, a superficial bacterial infection located in the genitocrural area, is caused by *Corynebacterium minutissimum*, and is more commonly found in men and obese persons with diabetes. Postoperative clean-wound infections have been reported to occur with increased frequency in diabetics.

### **Superficial Necrotizing Infections**

These infections do not extend below the deep fascia enveloping muscles. *Crepitant (anaerobic cellulitis)* infections are frequently superimposed on chronic, nonhealing

ulcers and are generally characterized by extensive subdermal and subcutaneous gas dissection produced by multiple organisms, particularly anaerobes. Good clinical outcome is generally seen with thorough debridement and appropriate antimicrobial therapy. *Necrotizing fasciitis* is characterized by extensive dissection of the infection along the superficial fascial planes without involvement of the underlying muscles. Although it may sometimes be caused by single organisms (such as *Streptococcus pyogenes*), mixed infections with aerobes and anaerobes are more frequently seen (i.e., *Bacteroides* spp., *Peptostreptococcus* spp., *E. coli*, *Proteus mirabilis*, *Enterococcus* spp., and so on) (39). Thrombosis of nutrient vessels to the skin may occur, resulting in patchy areas of skin gangrene. Bullae formation under the skin may develop in the later stages, but early disease may show little external changes (e.g., tautness of the skin, mild erythema, and tenderness). Patchy areas of skin anesthesia may occur secondary to the destruction of small nerve fibers to the skin in the later stages. Management includes thorough debridement and drainage of the necrotic fascia and the associated purulence (the so-called “filleting procedure,” where the subcutaneous tissue is left open and subjected to irrigation with normal saline or Ringer’s lactate solutions). When mixed infection is present, appropriate antimicrobial therapy should be directed toward both the aerobic and anaerobic flora. *S. pyogenes* infection is frequently associated with toxic shock syndrome. In this situation, addition of clindamycin to high-dose penicillin G has been suggested, primarily to halt the organism’s toxin production. Intravenous gamma globulin administration has also been felt to be helpful. Repeated surgical debridement is frequently required.

### Deep Necrotizing Infections

*Nonclostridial myonecrosis* (erstwhile known as necrotizing cellulitis) is an extensive infection, and up to 75% of these cases have been reported to be in diabetics. The bacterial flora involved are similar to necrotizing fasciitis, but infection involves the muscles. Therapy is similar, but resection of necrotic muscle is required. *Clostridial myonecrosis* related to injuries do not appear to occur more frequently in association with diabetes. However, there are some suggestions that the spontaneous or hematogenous form of this disease has a predilection to involve diabetics. *C. septicum* (not *perfringens*) is the organism generally involved, and there is a strong association with the presence of colonic malignancy. *Foot-related infections* may involve deep tissues. The major factors contributing to foot-related infections are diabetic neuropathy, vascular disease, and impaired immune resistance. Superficial and milder infections are frequently monomicrobial (usually from gram-positive cocci such as *S. aureus*), but more severe infections, associated with tissue necrosis and/or gangrene, is generally polymicrobial (aerobic and anaerobic) in origin (see Table 2). These infections may be associated with gas formation from the proliferation of gas-forming organisms such as *Bacteroides*, *Prevotella*, *Porphyromonas*, *Peptostreptococcus*, or even from the aerobic *E. coli*. Underlying osteomyelitis needs to be excluded, generally with an MRI scan, and the vascular

status may need to be determined by use of Doppler ultrasound with wave-form analysis or with transcutaneous oximetry. Milder infections (i.e., limited cellulitis) may be managed with thorough debridement of the infected wound and antimicrobial therapy. First- or second-generation cephalosporins such as cefazolin or cefuroxime may be used for presumed monomicrobial infections. For more serious infections broad-spectrum coverage is frequently indicated (i.e., parenteral piperacillin-tazobactam, imipenem, or tigecycline). The presence of osteomyelitis may require removal of infected bone (i.e., toe amputation, with or without ray resection). Amputation may sometimes be necessary, and the level is dictated by the extent of bone involvement, the status of the vascular supply, and the extent of soft-tissue involvement. In general, the extent of surgery needs to be balanced by thorough removal of infected tissue on the one hand and the preservation of ambulatory capability on the other (40, 41).

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# Vaccinations

Rex Biedenbender and Stefan Gravenstein

## Key Points

- People with advanced age experience greater morbidity and mortality from infectious diseases, due, in part, to immunosenescence.
- Older and vaccinated individuals present with attenuated symptoms and signs in many infections.
- When infection still occurs, vaccination remains cost effective to prevent infectious diseases or attenuate morbidity and mortality.
- Vaccination rates >80% reduce spread, morbidity, and mortality of some infections through herd immunity.
- Influenza, pneumococcal, tetanus/diphtheria, and herpes-zoster vaccinations are recommended for elders.

## Introduction: Aging, the Immune Response, and Vaccination

Complications and sequelae from infections increase with age. *Immunosenescence*, the cause of age-related decline of immune responsiveness, affects individual capacity to clear infections and respond to vaccines thereby reducing vaccine effectiveness (1, 2). Meanwhile, the dysregulated immune senescent response takes longer both to activate and to down-regulate. The longer duration of inflammation may lead to immunopathologic complications including tissue necrosis and thrombosis, resulting in diseases such as strokes or heart attacks (3). A significant proportion of strokes and heart attacks follow infectious events (3–5) and appear to be reduced by vaccination

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such as influenza (6). Examples of pathogens with specifically greater impact on elderly individuals include influenza (6), pneumococcal pneumonia, and recrudescing latent infections such as herpes zoster. Older people also suffer more frequently from toxin producing bacteria of *Clostridium difficile* and *C. tetani*. Vaccines are effective by inducing immune memory, shifting immunity from the less efficient and more inflammatory innate response to the faster adaptive immune response. This leads to more rapid clearing of infectious agents or toxin neutralization.

Because of immunosenescence alteration in host defenses, and multimorbidity, elderly individuals respond less efficiently to therapies and are more likely to be infected by unusual pathogens. Immunosenescence and vaccination also attenuates symptoms such as fever, due to reduction in the responses or effect of pyrogenic inflammatory cytokines, making timely diagnosis more difficult. Maintaining a high index of suspicion for infection in vaccinated and frail elders is just as important as typical symptoms and signs, as even leukocytosis may be greatly reduced or absent.

Despite the reduced immune response to vaccine by elderly individuals, vaccination significantly prevents or attenuates infectious disease and remains one of the most cost-effective strategies available (7, 8). In closed settings, if vaccination rate is high enough, then *herd immunity* is induced, significantly reducing spread of communicable diseases such as influenza.

This review focuses on vaccines for persons 65 years of age or older; the vaccines include the following: tetanus–diphtheria toxoid, influenza virus, *Streptococcus pneumoniae* (pneumococcal), and most recently herpes zoster (shingles). Current recommendations of the centers for disease control and prevention’s (CDC) advisory committee on immunization practices (ACIP) are also included (9). Other vaccines such as cholera, hepatitis A and B, meningococcal, pertussis, typhoid, rabies, yellow fever, and plague are recommended in special circumstances for example, exposure through occupational hazard or travel to an endemic area; however, these guidelines are not included here.

## Improving Vaccination Utilization

Despite evidence of reduced morbidity and mortality from vaccine preventable illnesses even in the frailest long-term care (LTC) populations, vaccination rates remain suboptimal. Some vaccine preventable illnesses have reduced incidence attributed to widespread immunization programs of children or military personnel. However, policies have not supported the same directed efforts for elderly patients, for whom vaccination has been largely voluntary, individual physician directed, or by individual LTC facility policy. For LTC facilities, acceptance of vaccine, offered through policies, has remained voluntary. Efforts to educate the public and health professionals have had mixed success, as certain misconceptions such as influenza vaccine causing influenza infection persist. Nevertheless, standing policies in LTC facilities to offer vaccinations without charge and other strategies have somewhat managed to improve

vaccine uptake (10). Also, employee health plans, which offer influenza vaccination in the workplace, have boosted vaccination rates; this is likely due to convenience. Point of care and physician reminders such as those available through exploitation of electronic health records and reminders to clinicians to recommend vaccination have also correlated with increasing vaccine uptake. This latter strategy is especially important for vaccines not administered annually for instance, tetanus. Short of standing orders and programmed electronic reminder systems, an accurate vaccination history plus a vigilant primary care provider, patient, or caregiver remain the mainstay approach to providing timely vaccinations and boosters.

## **Tetanus–Diphtheria Toxoid Vaccine**

Tetanus remains low in incidence but continues to cause serious health problems for older patients. Caused by the toxin produced by *Clostridium tetani*, tetanus occurs almost exclusively in unimmunized persons. With a puncture wound or laceration, patients seeking medical care need their tetanus vaccination status assessed to determine if tetanus toxoid or immune globulin are indicated. The risk of tetanus infection doubles in those 60 years old and older as compared with those aged 20–59 years (11). Risk of mortality increases with age. Elder patients are more at risk because of declining serum antibody levels to the tetanus extracellular neurotoxin, tetanospasmin. A U.S. population survey showed prevalent immunity in only 28% of those  $\geq 70$  years old as compared with 80% in younger individuals. An unknown history or history of receiving fewer than two doses of tetanus toxoid predicts non-protective titer levels.

Clinical manifestations of tetanus include prolonged spasms of flexor and extensor muscle groups. Progression to generalized flexion contractures and masseter muscle spasm (“lockjaw”) occurs in advanced cases. Involvement of the respiratory muscles leads to death by suffocation.

Diphtheria is caused by *Corynebacterium diphtheriae*. It is rare in the United States, with only a few cases reported per year. Widespread use of diphtheria toxoid limits annual incidence to virtually nil with greater than 90% of cases occurring in unimmunized adults.

### ***Vaccine Effectiveness***

Tetanus–diphtheria toxoids are some of the most immunogenic of approved adult vaccines. They are considered 100% effective for immunocompetent persons with up-to-date vaccination status. Natural immunity to tetanus does not occur, and natural immunity to diphtheria occurs in only 50% of cases. Primary vaccination with tetanus toxoid provides 10 or more years of protection. Diphtheria outbreaks abroad demonstrate persistent of diphtheria risk among under-immunized populations. In Sweden,

a reemergence of diphtheria occurred, mostly in patients at least 60 years old, after a 23-year period without reported cases. With the United States having a similar proportion of older adults without protective immunity as Sweden, a repeat of the Swedish experience of re-emergent diphtheria looms.

### ***Indications***

Adults who have not been immunized should be immunized against both tetanus and diphtheria with the initial primary series. Earlier doses do not need repeating if the schedule is delayed. Those who have not completed the primary series should finish it with combined Td vaccine, and receive revaccination every 10 years thereafter. A booster dose even years later after primary vaccination still provides protection. Up-to-date vaccination status is especially important if travel to developing countries is anticipated. Tetanus–diphtheria toxoid (Td) prophylaxis is recommended for clean, minor wounds if the primary series is incomplete or the last booster vaccination was more than 10 years ago. Serious wounds require added passive immunization with tetanus immune globulin. Cost effectiveness of tetanus immunization, specifically booster doses, has been questioned. Because tetanus is rare, the cost of each case prevented and associated year of life gained is high. Some experts have recommended targeting only high-risk adults for revaccination for example, those with vascular ulcers at time of injury.

### ***Administration and Revaccination***

Tetanus toxoid (TT) is produced singly or in combination with diphtheria toxoid (Td) and with or without whole-cell or acellular pertussis vaccine. In older adults, Td is recommended. The primary series vaccination for adults consists of two 0.5-ml doses of Td given intramuscularly (IM) 1–2 months apart, followed by a third 0.5-ml dose, given 6–12 months later. The Td vaccine contains 10% of the diphtheria toxoid in the pediatric DTP, making it much less reactogenic for adverse events.

### ***Adverse Reactions***

Everyone present vaccines are well tolerated by most individuals. The pertussis component has historically caused the majority of the reactogenicity of childhood DTP vaccines; reformulation to an acellular pertussis antigen has substantially reduced reactogenicity. Sensitivity to the preservative or a history of neurological or severe hypersensitivity reaction following diphtheria or tetanus vaccination remain as contraindications to TT and Td vaccination. Side effects include local reactions, fever, chills, hypersensitivity, arthralgia, rash, and encephalopathy. Local reactions to the vaccine remain common, occurring in 40–50% of previously immunized adults.

## **Influenza Vaccines**

Currently, those aged 65 years and older account for over 90% of the deaths attributed to pneumonia and influenza (12). For the reasons described in the introduction, including immune senescence and impaired viral clearance, elderly individuals experience increased risk for influenza complications such as bacterial superinfection and mortality. Since influenza vaccination rates have increased from 20% of the population some 20 years ago to over 70% in recent years, its rank, by 2005, as a leading cause of death has declined from fourth to seventh. The influenza-related deaths from 19 epidemics occurring from 1972–1973 through 1994–1995, ranged from 30 to 150 per 100,000 persons aged 65 years and older. Influenza-related illness still costs more in healthcare dollars and claims more lost lives than any other viral illness in the United States (13). Due to the high attack rate and aging population, influenza's impact is likely to increase unless better control of influenza is attained (see also chapter "Viral Infections").

Influenza outbreaks relate to two phenomena: antigenic drift and antigenic shift. Recombination of genetic segments produce antigenic shift, while single nucleic acid substitutions in the genome causes antigenic drift. These phenomena allow the virus to escape immune recognition, which permits annual epidemics with antigenic drift or the characteristically more serious pandemics every few decades with antigenic shift.

### ***Vaccine Effectiveness***

Vaccination is far more cost effective than chemoprophylaxis with antiviral agents. Well-matched vaccines reduce the incidence and the severity of influenza illness; however, poorly matched vaccines still are beneficial. Vaccinations reduce influenza-related hospitalizations, radiologically diagnosed cases of pneumonia, events related to strokes and ischemic heart disease (14), and deaths. Immunosenescence, poor vaccine immunogenicity, and poorly matched vaccine all reduce vaccine-derived protection. Due to immunosenescence and multimorbidity, some healthy elderly and one-half of institutionalized individuals fail to develop "protective" vaccine-induced antibody titers as compared with 70–90% of young healthy adults; fewer develop substantial cellular immunity. Supplemental "booster" vaccination and vaccines have not consistently yielded increased antibody response (immunogenicity) in elderly persons but have shown more side effects (reactogenicity). However, despite developing only low antibody titers, elderly persons still benefit from vaccination; symptoms remain less severe and the risk of complications, hospitalization, and death is reduced (15).

### ***Indications***

Annual vaccination is recommended for high-risk individuals, for their caregivers, and for those in close contact with high-risk person. High-risk individuals include LTCF residents, persons  $\geq 50$  years old, persons with chronic pulmonary or

cardiovascular disorders, and persons requiring frequent follow-up or hospitalization during the preceding year due to chronic metabolic disorders, renal dysfunction, hemoglobinopathies, or immunosuppression. Children 6 months to 5 years old and pregnant women are now also recommended to receive vaccination (9).

### *Administration and Revaccination*

Intramuscular (IM) injection of 0.5 ml of the trivalent influenza vaccine using a 1 in. or longer needle is recommended in the United States for those age  $\geq 50$ . Due to reduced muscle and increased fat, half-inch needles may fail to reach muscle. Subcutaneous (SC) and intradermal (ID) routes have been used but efficacy is not adequately proven. Live attenuated influenza vaccine (LAIV) is now available (i.e., Flumist™, MedImmune, Inc.) but is approved only for those ages 5–49 years and, in many chronic conditions, is specifically contraindicated. Due to the virus' rapid antigenic changes, annual vaccination is needed.

Optimum timing of vaccination is important but not easily determined. Vaccination administered too early may result in antibody titers falling prior to virus circulation. Late vaccination permits viral exposure before a protective antibody develops. Vaccination in November is reasonable, but before October it is usually premature except in tropical (e.g., Caribbean) and sub-Arctic and Arctic climates (e.g., Alaska). Influenza typically circulates from December to March, justifying a January or a later vaccination for those who have not already been immunized. Healthcare professionals in all settings of care should also be vaccinated. Upon identification of an influenza outbreak in LTCFs, the vaccine should be re-offered to unvaccinated staff and residents. Adjunctive therapy with an antiviral agent for 2 weeks following vaccination allows time to develop vaccine-induced immunity. Unvaccinated persons should be offered chemoprophylaxis with an approved influenza antiviral. Since 2004, there has been substantial circulating influenza resistant to the adamantane class of antivirals (16, 17), making the neuraminidase inhibitors the preferred alternative. Recent reports of resistance to oseltamivir but not zanamivir have also appeared, potentially affecting future antiviral choice (18). Dosing information is presented in Table 1.

**Table 1** Daily dosage of influenza antiviral medications for prophylaxis in LTCF residents during an outbreak

Antiviral agent <sup>a</sup>	Daily dose	Duration
Zanamivir <sup>b</sup>	10 mg/day	7–10 days
Oseltamivir <sup>c</sup>	75 mg/day	7–10 days

<sup>a</sup>Adamantanes are not currently recommended for treatment of influenza A/H3N2 due to widespread resistance to these strains. Adamantanes are not effective against influenza B.

<sup>b</sup>Zanamivir and oseltamivir are approved for prophylaxis in family settings as one-half the daily dose  $\times$  10 days.

<sup>c</sup>Influenza A/H1N1 resistance to oseltamivir was widespread for the 2008–2009 season.

## Safety

Fear of adverse effects has reduced vaccination rates. All currently available vaccines for those individuals aged 50 years or older contain only non-infectious particles, and, therefore, the vaccines cannot cause an influenza infection. Respiratory illness occurring after vaccination is coincidental. About 30% of recipients have injection site tenderness for up to 2 days post-vaccination. Fever, malaise, or myalgia occurs in only a few percent of individuals, and most commonly in those who are naïve to the influenza vaccine. Systemic reactions in elderly people occur in frequency similar to those receiving placebo. Rare hypersensitivity reactions to vaccine components, residual egg proteins, or preservatives do occur. Influenza vaccine should not be given to those individuals with anaphylactic hypersensitivity to eggs. Only the 1976 influenza vaccine was significantly associated with Guillain–Barre’ syndrome but only for a frequency under 1/1,000,000 vaccinated.

The remote possibility of influenza viral transmission from staff vaccinated with LAIV to residents has generated substantial discussion. Currently, the CDC recommends staff and visitors receiving LAIV to avoid contact with *severely* immune compromised patients for 7 days. Viral shedding from healthy adults aged 18–49 years who received LAIV reportedly generally resolves within 3 days, but can last up to 10 days (19). Previous recommendations to avoid all potentially immune suppressed contacts for 21 days following LAIV administration have been demonstrated to be unnecessary.

## Pneumococcal Vaccines

*Streptococcus pneumoniae*, a gram-positive bacterium, also referred to as pneumococcus and diplococcus colonizes the nasopharynx. Isolated from the nasopharynx in up to 70% prior to the widespread availability of antibiotics, *S. pneumoniae* now colonizes fewer than 40%. Concurrently, pneumococci, also have lost their universal sensitivity to penicillin (20, 21). The growing penicillin resistance has implications for antimicrobial treatment and it also reinforces the need to focus on prevention as the primary approach to reducing *S. pneumoniae*-related disease. *S. pneumoniae* is generally harmless in the nasopharynx; however, when it invades the lung, pneumonitis progresses to pneumonia and to death if there is no rapid intervention. Prevention of pneumococcal disease holds great promise for impacting outcomes in elderly and immune-compromised populations.

Invasive *S. pneumoniae*, in adults, causes one-third of community-acquired pneumonia and one-half of hospital-acquired pneumonia, and 60,000 cases of invasive disease annually. Other consequences of invasive pneumococci include bacteremia, otitis media, sinusitis, meningitis, septic arthritis, pericarditis, endocarditis, peritonitis, cellulitis, glomerulonephritis, and sepsis (especially post-splenectomy). Mortality from pneumococcal disease increases from under 40% among those from 50 years old up to 70 years old to over 55% for those over 70 years of old (22). Most commonly, those who die most have bacteremia or meningitis.



## ***Pneumococcal Vaccine***

Studies have supported claims of efficacy and cost effectiveness of the current 23-valent vaccine for preventing pneumonia and bacteremia in elderly persons (23). The Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention recommends (ACIP/CDC) pneumococcal vaccine for the individuals at risk for pneumococcal disease (see Table 2) (23). Revaccination is recommended for persons at least 65 years old if they have been vaccinated 5 or more years previously and were also under 65 years old at the time of vaccination(9).

The currently available 23-valent vaccine is Pneumovax® 23, a Merck and Company product. It contains 25 mcg of capsular polysaccharide antigen for each of the 23 most prevalent and pathogenic *S. pneumoniae* serotypes in a 0.5 ml dose, covering 90% of blood isolates and 85% of pneumococcal isolates in the United States

## ***Efficacy***

The Veterans Administration (now called Department of Veterans Affairs) Cooperative Study remains among the few randomized controlled trials of pneumococcal vaccine efficacy as measured by both clinical and serologic terms (24). However, this study has been criticized for lack of power to draw generalized conclusions. In a study population of 2,295, one case of pneumococcal infection in 1,175 vaccine recipients was observed, while 42 infections of proven and probable cause were identified in the control group. In two other trials conducted in individuals >50 years of age, efficacy was 69% and 70%, respectively. A 1982–1985 population-based cohort study in Finland compared pneumococcal and influenza vaccination to influenza vaccine alone. This study claimed a protective efficacy against pneumonia of 71% in individuals over 70 years of age with an additional risk (other than age alone) for contracting pneumonia (25). Additional risks included those with heart disease, lung disease, bronchial asthma, alcoholism, or those who were institutionalized or permanently bedridden. Due to limitations of the study design, experts questioned the validity because of the ability to generalize not only with this study but also with virtually all of the studies performed to date (26). The most consistent results for protective efficacy have been for prevention of pneumococcal bacteremia.

## ***Antibody Response***

Vaccine efficacy can also be assessed by antibody response to vaccination. In theory, if an individual develops antibody response to a vaccine antigen, they are protected from infection. Most healthy adults generate a satisfactory antibody response to serotypes in pneumococcal vaccine. High-risk populations, however, have inconsistent antibody response. In immunocompromised adults, or who are  $\geq 65$  years of age, antibody

**Table 2** Recommendations for adult immunization

Vaccine (and route)	For whom it is recommended	Schedule	Contraindications and precautions (mild illness is not a contraindication)
Influenza (Give IM Inactivated)	<ul style="list-style-type: none"> <li>Adults who are 50 years of age or older</li> <li>Adults &lt;50 years of age with medical problems such as heart disease, lung disease, diabetes, renal dysfunction, hemoglobinopathies, immunosuppression, and/or those living in chronic care facilities</li> <li>People working or living with at-risk people</li> <li>All healthcare workers and those who provide key community services</li> </ul>	<ul style="list-style-type: none"> <li>Given every year</li> <li>October through November is the optimal time to receive an annual flu shot to maximize protection, but the vaccine may be given at any time during the influenza season (typically December through March) or at other times when the risk of influenza exists</li> <li>May be given anytime during the influenza season</li> <li>May be given with all other vaccines but at a separate site</li> </ul>	<ul style="list-style-type: none"> <li>Previous anaphylactic reaction to this vaccine, to any of its components, or to eggs</li> <li>Moderate or severe acute illness</li> </ul>
Pneumococcal polysaccharide (Give IM or SQ)	<ul style="list-style-type: none"> <li>Adults who are 65 years of age or older</li> <li>Adults &lt; 65 years of age who have chronic illness or other risk factors including chronic cardiac or pulmonary diseases, chronic liver disease, alcoholism, diabetes mellitus, CSF leaks, as well as persons living in special environments or social settings (including Alaska natives and certain American Indian populations). Those at highest risk of fatal pneumococcal infection are persons with anatomic or functional asplenia, sickle cell disease, immunocompromised persons including those with HIV infection, leukemia, lymphoma, Hodgkin's disease, multiple myeloma, generalized malignancy, chronic renal failure, or nephrotic syndrome, those receiving immunosuppressive chemotherapy (including corticosteroids), and those who received an organ or bone marrow transplant</li> </ul>	<ul style="list-style-type: none"> <li>Routinely given as a one-time dose; administer if previous vaccination history is unknown</li> <li>One-time revaccination is recommended 5 years later for people at highest risk of fatal pneumococcal infection or rapid antibody loss (e.g., renal disease) and for people ≥65 years if the first dose was given prior to age 65 and ≥ 5 years have elapsed since previous dose</li> <li>May be given with all other vaccines but at a separate site</li> </ul>	<ul style="list-style-type: none"> <li>Previous anaphylactic reaction to this vaccine or to any of its components</li> <li>Moderate or severe acute illness</li> </ul>

(continued)

**Table 2** (continued)

Vaccine (and route)	For whom it is recommended	Schedule	Contraindications and precautions (mild illness is not a contraindication)
Td (Tetanus, diphtheria) (Give IM)	<ul style="list-style-type: none"> <li>All adolescents and adults</li> <li>After the primary series has been completed, a booster dose is recommended every 10 years. Determine if patients have received a primary series of three doses</li> <li>A booster dose as early as 5 years later may be needed for the purpose of wound management</li> </ul>	<ul style="list-style-type: none"> <li>Booster dose every 10 years after completion of the primary series of three doses</li> <li>For those who have fallen behind:               <ul style="list-style-type: none"> <li>The primary series is three doses</li> <li>Give dose #2 four weeks after #1</li> <li>#3 is given 6–12 months after #2</li> </ul> </li> <li>May be given with all other vaccines but at a separate site</li> <li>Two doses are needed</li> <li>Dose #2 is given 4–8 weeks after dose #1</li> </ul>	<ul style="list-style-type: none"> <li>Previous anaphylactic or neurologic reaction to this vaccine or to any of its components</li> <li>Moderate or severe acute illness</li> </ul>
Varicella (Chicken Pox) (Give SQ)	<ul style="list-style-type: none"> <li>All susceptible adults and adolescents (those not having had chicken pox) should be vaccinated. Make special efforts to vaccinate susceptible persons who have close contact with persons at high risk for serious complications (e.g., healthcare workers and family contacts of immunocompromised persons) and susceptible persons who are at high risk of exposure (e.g., teachers of young children, day care employees, residents, and staff in institutional settings such as colleges and correctional institutions, military personnel, adolescents, and adults living with children, non-pregnant women of childbearing age, and international travelers who do not have evidence of immunity). Note: People with reliable histories of chickenpox (such as self or parental report of disease) can be assumed to be immune. For adults who have no reliable history, serologic testing may be cost effective since most adults with a negative or uncertain history of varicella are immune</li> </ul>	<ul style="list-style-type: none"> <li>Two doses are needed</li> <li>Dose #2 is given 4–8 weeks after dose #1</li> </ul>	<ul style="list-style-type: none"> <li>Previous anaphylactic reaction to this vaccine or to any of its components</li> <li>Pregnancy, or possibility of pregnancy within 1 month</li> </ul>

- May be given with all other vaccines but at a separate site
- If varicella vaccine and MMR are both needed and are not administered on the same day, space them at least 4 weeks apart
- If the second dose is delayed, do not repeat dose #1. Just give dose #2
- Immunocompromised persons due to malignancies and primary or acquired cellular immunodeficiency including HIV/AIDS. Note: For those on high dose immunosuppressive therapy, consult ACIP recommendations regarding delay time
- If blood products or immune globulin have been administered during the past 5 months, consult the ACIP recommendations regarding time to wait before vaccinating
- Moderate or severe acute illness. Note: Manufacturer recommends that salicylates be avoided for 6 weeks after receiving the varicella vaccine because of a theoretical risk of Reyes syndrome

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(continued)

**Table 2** (continued)

Vaccine (and route)	For whom it is recommended	Schedule	Contraindications and precautions (mild illness is not a contraindication)
Varicella (Shingles) (Give SQ)	<ul style="list-style-type: none"><li>Indicated for the prevention of herpes zoster (shingles) in individuals age 60 and older</li><li>Not indicated for the treatment of acute shingles or post herpetic neuralgia</li></ul>	<ul style="list-style-type: none"><li>Given as a one-time dose</li></ul>	<ul style="list-style-type: none"><li>History of anaphylactic/anaphylactoid reaction to gelatin, neomycin, or any other component of the vaccine</li><li>History of primary or acquired immunodeficiency states</li><li>On immunosuppressive therapy</li><li>Not indicated in women of child bearing age and should not be given to pregnant females</li></ul>

*IM* intramuscular, *SQ* subcutaneous, *CSF* cerebrospinal fluid, *HIV* human immunodeficiency virus, *MMR* mumps, measles, rubella; *AIDS* acquired immunodeficiency syndrome; (Reference 27)

responses have been variable. Healthy elderly patients have been observed to have lower antibody responses compared with the responses in young, healthy adults.

The currently available pneumococcal vaccine for adults contains purified capsular polysaccharide antigens. Current protein conjugate vaccines (e.g., Prevnar®) are already on the market place, but they have not been approved for use in adults.

## ***Safety***

Currently available pneumococcal vaccines are safe with reactions to initial administration causing erythema and pain at injection site in 50%; fever, myalgia, and severe local reactions <1%, and anaphylaxis has been reported to occur in five cases per million. Although not an official ACIP/CDC recommendation, the authors of this chapter suggest revaccination should be considered for those persons who are at highest risk for pneumococcal disease and complications.

## **Drug Interactions**

Administration of pneumococcal and influenza vaccines in separate IM sites has not caused increased adverse effects or reduced immunogenicity and is accepted by the CDC, when necessary to administer two or more vaccines concurrently.

## ***Herpes-Zoster Vaccine***

Varicella zoster virus causes herpes zoster or shingles, which is the same virus that causes chicken pox (see also chapter “Herpes Zoster”). In the initial VZV infection, the VZV becomes dormant in the dorsal root ganglion until underlying immune compromise or stress allows for viral reactivation, which often occurs many decades later. Herpes zoster typically presents as a unilateral painful viral exanthem in elderly, immunocompromised, or stressed individuals. The exanthem erupts as a cluster of blisters following one or more (as many as 21) days of pain typically along a dermatome. The pain can be burning, itching, hypesthetic, stinging, tingling, aching or throbbing, often confounding the clinician until the rash appears and is followed by an eruption of blisters along the symptomatic dermatome. Other nonspecific symptoms may be present, including fever, headache or malaise, and some patients fail to develop the classic rash. Some unfortunate individuals have their virus stored in the ganglion of a cranial nerve. When the latent herpes virus reactivates from the trigeminal nerve, as occurs in 10–25% of cases, it can cause conjunctivitis, keratitis, uveitis, optic nerve palsy and blindness, or trigeminal neuralgia. Reactivation from the seventh to eighth cranial nerve can cause Ramsay Hunt syndrome with vertigo and hearing loss.

Although herpes zoster can occur at any age, most who acquire the infection are over the age of 50, and follows a decline in cell-mediated immunity. The VZV virus

replicates in the nerve cell and can spread from open blisters and rash to others via direct contact. Those who come into contact with the virus will develop chicken pox, if not previously infected, but otherwise they will be immune. Herpes zoster can recur, but rarely will it reactivate up to three times, and sometimes it will recur but without the accompanying rash and generally with pain along the same dermatome as the original eruption. The morbidity from the cranial neuropathies, polyneuritis, aseptic meningitis, and myelitis can cause permanent damage to the affected nerve or encephalitis. The annual rate of herpes zoster approaches 1.4% of elderly, and, in nearly half of these, post-herpetic neuralgia develops. Sequelae such as post-herpetic neuralgia occur most commonly in those over age 50.

Until recently, treatment was limited to a reactive approach of acyclovir or its prodrug valacyclovir with or without corticosteroids. In May of 2007, the Food and Drug Administration (FDA) approved the varicella-zoster vaccine, Zostavax<sup>®</sup>, for use in herpes zoster prevention or for those immunocompetent individuals aged 60 years or older (27).

### ***Vaccine Effectiveness***

The FDA approval of Zostavax followed after the Shingles Prevention Study of nearly 40,000 adults over 60 years old, who were followed on average of more than 3 years (28). Herpes zoster incidence declined by 51%, and, among vaccine recipients, the zoster sequelae by 61%. However, the lowest efficacy occurred among those 80 years and older, who had a preventive efficacy of 18%; this group also had only a 26% reduction in postherpetic neuralgia and it was even less among those over age 85 (29, 30). The vaccine has not been adequately studied among those who have immune compromise, immune suppression, malignancy, life-expectancy less than 5 years, or with multimorbidity, who all belong to groups where vaccine efficacy would likely be reduced.

### ***Indications***

Zostavax is a live attenuated virus vaccine indicated for prevention of herpes zoster (shingles) in individuals 60 years of age and older. It is not indicated for the treatment of herpes zoster or postherpetic neuralgia.

### ***Administration and Revaccination***

Zostavax should be administered as a single 0.65 mL dose subcutaneously in the deltoid region of the upper arm, through a single-use, sterile preservative, and detergent-free syringe.

### ***Preparation for Administration***

Zostavax is stored frozen and should be reconstituted immediately upon removal from the freezer. The diluent should be stored separately at room temperature or in the refrigerator. Using separate sterile needles for reconstitution and administration of Zostavax, inject all of the diluent supplied into the vial of lyophilized vaccine and gently agitate to mix thoroughly. Withdraw the entire reconstituted (semi-hazy to translucent) vaccine into a syringe and, immediately after reconstitution, inject the total volume subcutaneously to avoid potency loss. If the vaccine is not used within 30 min, then discard the reconstituted vaccine. The reconstituted vaccine should not be re-frozen.

### ***Adverse Reactions***

In the Shingles Prevention Study, there were serious adverse events that occurred, in equal frequency, except in the 80 years old and older group. In the oldest groups among vaccine recipients, cardiac events occurred slightly more frequently, including heart failure and pulmonary edema. Adverse events occurred in all vaccine recipient groups 20–100% more often from youngest to oldest, and most of these were injection-site related.

### ***Cost-Effectiveness***

A 2007 study estimated vaccine cost-effectiveness to range from \$16,229 to \$27,609 per quality-adjusted life year gained and projected an annual savings of \$82 to \$103 million in healthcare costs for 1 million healthy vaccine recipients over age 60 (31). The cost avoidance calculation included reduced outpatient visits, prescriptions, ER visits, and hospitalizations. The limitations of the calculation relate to the limitations of the Shingles Prevention Study, where most of the benefits would accrue to the youngest recipients.

### ***Contraindications***

Zostavax is contraindicated for those individuals with a history of anaphylactoid reaction to gelatin, neomycin, or any other component of the vaccine (can you clarify whether the following groups of people are also at risk) human immunodeficiency virus infection; immunosuppressive therapy; or women of childbearing age or who are pregnant.



## ***Warnings***

Viral transmission can occur between vaccinees and susceptible contacts. The vaccine is not indicated to prevent chickenpox (the vaccine contains the same virus as the licensed chickenpox vaccine, but has 14 times the infectivity). Protection beyond 4 years remains unknown. Vaccination should be deferred in patients with active untreated tuberculosis, or other acute infections, especially if febrile.

## ***Drug Interactions***

The vaccine should not be co-administered with drugs used to treat shingles or chicken pox.

## **Vaccinations of Health Care Workers**

Immunization of healthcare staff is recommended to prevent spread of infection to frail elders, as healthcare workers can serve as vectors for disease transmission. The recommended vaccination rate for staff with direct patient contact is 80%. Immunization rates even in LTCF remain low despite these recommendations.

Potter et al. evaluated effects of vaccinating healthcare staff in geriatric LTC hospitals on incidence of influenza, lower respiratory tract infections, and death (32). When staff were vaccinated, influenza-like illness occurred in 7.7% of unvaccinated patients as compared with 0.9% of vaccinated patients. Fewer patients died in hospitals where healthcare staff were vaccinated than where they were not vaccinated (10% vs. 17%, respectively).

Clinical data on efficacy of healthcare staff vaccination with respect to resident benefit is primarily on influenza vaccination. It is still reasonable to encourage pneumococcal vaccination to reduce carriage of pathogenic and antibiotic-resistant strains; and, in addition to annual influenza vaccination, it is also reasonable to encourage hepatitis vaccination to protect staff. To maximize compliance, vaccination should be free to employees; vaccine status should be reviewed upon employment and, also annually at the time influenza vaccination (10). A formal policy of vaccination status review and annual education regarding importance of vaccination to staff and residents will help people to comply. Policy review and enforcement should be assigned to the infection control practitioner, backed with authority from administration, and remain consistent with local, state, and federal statutes.

## Summary

Vaccination remains the most cost-effective prevention strategy for a variety of infectious diseases afflicting the elderly population. Given numerous factors that limit timely diagnosis of infectious disease in the elderly (e.g., immune senescence, decreased access to medical facilities, etc.) and also the higher morbidity and mortality resulting from infections in this population, prevention strategies focusing on immunization are prudent. Counteracting the mild immune-deficiency by priming it to react faster and more robustly to infectious challenges has proven an effective strategy against vaccine-preventable disease. Vaccination rates among older adults are still suboptimal, primarily due to lack of concerted efforts of physicians and healthcare systems, lack of governmental mandate as in pediatric populations, and patient apathy. In the case of communicable diseases, studies show the benefit to both individual vaccine recipients and to the patient's contacts. For highly transmissible diseases such as influenza, caregivers should also be immunized in order to decrease vector transmission. Older adults, at specific occupational or travel risks, may have additionally recommended immunizations to protect them.

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# Nutrition and Infection

Kevin P. High

## Key Points

- Though global (protein/calorie) malnutrition is rare in the United States outside of those with wasting illnesses (e.g., cancer), macro- and micro-nutrient deficiencies (i.e., specific vitamins or minerals) are common in older adults, particularly those with multiple comorbidities or who live in long-term care facilities.
- Simple screening tools, such as serial weight measures or the body mass index can rapidly identify older adults at risk for nutritional deficiency.
- Clinical studies often use different populations, methods and outcome measures leading to widely varying results. Overall, however, there are little data to support general use of multivitamin/mineral or other nutritional supplements to prevent infection in the general population of older adults. Specific micronutrient supplementation, particularly multivitamin/mineral supplements with zinc and selenium, may be of value in some older adults in the long-term care setting.
- Some data suggest nutritional supplements (i.e., commercial liquid formulations) may be of benefit during acute infectious illness and/or convalescence.
- Evidence of harm due to over-supplementation is significant for vitamin A (increased risk of fractures) and for vitamin E (overall mortality); thus, micro-nutrients should not be considered harmless and doses above the age-adjusted recommendations should be discouraged.

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## Epidemiology and Clinical Relevance

Nutritional factors have been long established to play a major role in infection risk (1). Global (i.e., protein/calorie) malnutrition is rare in the United States and other industrialized countries. Similarly, micronutrient deficiencies to the degree required to cause recognized symptoms of deficiency previously identified in the developing world (e.g., blindness due to vitamin A deficiency) are quite uncommon in developed countries. The serum or tissue level required for optimal physiologic functions is unknown for most nutrients, and many nutrients demonstrate a “J-shaped” curve with poor outcomes both at very low and very high levels, thus, defining deficiency becomes a difficult task. However, older adults clearly comprise an “at-risk” population for malnutrition (Tables 1 and 2). Nutritional intake is often reduced in older adults by comorbidities such as dental disorders, stroke, dementia, or cancer. Contrary to commonly held notions, some nutrient requirements increase with age. Furthermore, elderly adults often live alone, may rarely prepare food for themselves, substitute cheaper foods in place of more expensive but more nutritious foods, or live in nursing homes or are homebound with minimal sunlight exposure (that may lead to reduced vitamin D synthesis).

Unapparent or “subclinical” malnutrition has been suggested to mediate, at least in part, immune dysfunction and the associated increased risk of infection in older adults (2). A variety of nutrients directly and indirectly influence immune function and presumably infection risk (3). Many nutritional supplementation studies utilize immune markers in older populations as a surrogate for infection risk, but adequately powered, well-designed studies are few and when performed have shown little evidence of reducing infection rates or use of antibiotics. Further, because of significant differences in study design, outcome measures, and even publication of fraudulent data, robust meta-analyses have been difficult (4). This chapter outlines the prevalence of malnutrition, keys for clinical assessment of at-risk older adults, and the major clinical trials of relevance in this area.

**Table 1** Common nutritional deficiencies in the elderly

Nutrient	Estimated prevalence <sup>a</sup>		Physical symptoms and signs and laboratory evidence of deficiency
	NH/Hosp (%)	Comm (%)	
Protein/calorie	17–65	10–25	Anorexia, depression, muscle wasting, dermatitis, depression, peripheral edema, low serum albumin, lymphopenia
Vitamin A	2–20	2–8	Skin dryness, corneal changes, night blindness
Vitamin B <sub>12</sub>		7–15	Dementia, depression, neuropathy, megaloblastic anemia
Vitamin D	20–40	2–10	Weakness, osteoporosis/osteomalacia
Vitamin E	5–15		Cerebellar ataxia, decreased reflexes, myopathy
Zinc	30	15–25	Loss of taste, lethargy, poor wound healing

<sup>a</sup>True prevalence is difficult to estimate and dependent on measure employed (i.e., intake, serum levels, tissue levels, change in physiologic measures). See text

NH nursing home, Hosp hospital, Comm community

**Table 2** Metabolic changes with aging and risk factors for malnutrition in the elderly

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Increased protein requirement
Decreased protein synthesis
Decreased nitrogen retention
Increased micronutrient requirement
Synthesis of vitamin D in the skin declines
Decreased renal hydroxylation of vitamin D to dihydroxyvitamin D
Atrophic gastritis and decreased stomach acid decreases absorption of vitamin B <sub>12</sub> , calcium, iron, and folate
Decreased nutrient intake
Loss of taste and smell
Food avoidance: milk products, limited menu
Dental disorders/ill-fitting dentures
Comorbidities (e.g., chronic obstructive pulmonary disease, congestive heart failure, cancer, depression, dementia)
Social isolation/living alone; rarely prepare meals
Economic factors: choosing between medications/food/rent
Medications: digoxin/other appetite suppressants

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## ***Global Malnutrition***

Global malnutrition (decreased intake or increased requirements for protein and calories) is the most common nutritional deficit of elderly subjects. Among older patients admitted to acute care hospitals or chronic care facilities, up to 65% are undernourished. This malnutrition is associated with significant adverse clinical outcomes. Volkert and colleagues (5) found a close correlation between nutritional status on admission and subsequent risk of hospital death, but the association remained after hospital discharge and the mortality rate remained higher over an 18-month follow-up. Sullivan and Walls (6) also found an increased risk of morbidity and mortality in undernourished elderly admitted to a Veterans Affairs (VA) geriatric rehabilitation unit (GRU), and further demonstrated that much of the risk is due to infection. Of 96 medical, functional, socioeconomic, and nutritional variables examined, only five were found to be associated with life-threatening complications; three of which were nutritional (serum albumin, body mass index, and amount of weight loss in the prior year; the other two variables were renal function and activities of daily living). Seventy-one life-threatening events occurred, of which 28 (39%) were clearly infectious (complicated pneumonia or sepsis). These authors further validated their model in a prospective cohort and found the five variables used in a model to be sensitive, specific, and 65% accurate for predicting life-threatening events. Thus, it appears that evidence of malnutrition is a strong predictor of morbidity and mortality in older, institutionalized adults.

If not present at the time of admission, undernutrition frequently complicates hospitalization of older adults. In a prospective study of a VA population (98% male) (7) 497 patients who were well nourished at the time of admission to an acute care hospital were followed after admission to the medical or surgical service. One hundred two of these patients (21%) had an average daily in-hospital nutrient

intake <50% of their calculated caloric needs. As expected, the undernourished group had lower discharge values for serum cholesterol, albumin, and pre-albumin, and lost slightly more weight than the well nourished group. Importantly, this group also experienced higher risk of death in-hospital (relative risk [RR] 8.0, 95% confidence interval [CI] [2.8–22.6]) and at 90 days (RR = 2.9 [1.4–6.1]), and were more likely than their well-nourished counterparts to require discharge to a nursing or rehabilitation facility (RR = 2.3 [1.1–4.6]). Major contributing factors to the undernutrition of hospitalized elderly included: “nothing by mouth” orders without nutrition via another route and ineffective use of canned supplements and nutritional support services. The major flaw in this observational cohort study is that it does not distinguish whether the undernutrition caused the adverse events or whether sicker patients were more likely to have poor intake and adverse outcomes (i.e., a confounding relationship). If anything, the undernourished group appeared to be healthier at baseline than the well-nourished group (more likely to have been admitted electively and better self-assessment of baseline health).

Other recent studies suggest that undernutrition is not confined to hospitalized elderly, but occurs in community-dwelling, apparently healthy elderly. Wilson and colleagues (8) reviewed the records of 1,017 outpatients in St. Louis and found evidence of undernutrition in 85 (8%). The elderly (age  $\geq$  65 years) were more likely to be undernourished than younger subjects (11% vs 7%, RR = 1.6 [1.5–2.51]). Undernutrition was only recognized 43% of the time in older adults, and only 14% had an intervention to correct the underlying cause. Intentional weight loss and a prescribed diet were the most common causes of undernutrition in younger patients, but rare in the elderly. Depression (30%), poorly controlled diabetes mellitus (9%), cancer (9%), oropharyngeal disease (7%), dementia (5%), and drug reactions (3%) were common, potentially treatable causes of poor nutrition in the older adult population.

### ***Micronutrient Deficiency***

Micronutrients can be broadly classified into vitamins (e.g., vitamins A, B-complex, C, D, E) and trace elements (e.g., zinc, selenium). Estimating the prevalence of micro-nutrient deficiencies in the elderly is difficult and “adequacy” may depend on the outcome measured. For example, vitamin A, a fat-soluble vitamin stored in the liver, is essential for both ocular health and immune function. A study of long-term care residents evaluated four measures of vitamin A deficiency in elderly adults: oral intake, urinary excretion in response to an oral vitamin A load, corneal cytology, and serum levels (9). These measures assessed vitamin A deficiency to be present in 55%, 21%, 6%, and 2% of facility residents, respectively. The relevant serum level to determine vitamin A deficiency is also unclear.

Vitamin E deficiency has been similarly difficult to define – often dietary intake is used, but serum levels can be measured. Since the optimal serum level is not known for vitamin E and there are many other forms of tocopherol that may have biologic activity (vitamin E is  $\alpha$ -tocopherol) associations with “deficiency” are frequently defined in populations by examining ordinal groups. For example,



a recent study demonstrated that serum vitamin E was strongly associated with risk of physical function decline in older adults by determining risk in each quartile (10).

Vitamin D deficiency is particularly common in the elderly due to a combination of social factors. Inadequate dietary intake (due to decreased consumption of milk and other dairy products) may be compounded by minimal sunlight exposure. A 1995 U.S. study (11) suggested that 54% of homebound and 38% of nursing facility resident elderly were vitamin D deficient by serum measures (i.e., serum concentration < 25 nmol/L).

Atrophic gastritis, present in up to one-third of elderly adults, is associated with vitamin B<sub>12</sub> deficiency and likely accounts for a significant number of the 7–15% of older adults in whom serum B<sub>12</sub> levels are low.

Two trace elements, zinc and selenium, have received significant attention in recent years with regard to immune function and deserve comment. Zinc intake falls throughout life and declines below the U.S. recommended dietary allowance (RDA) of 0.2 mg/kg (12–15 mg/day) in the majority of older adults. One study of healthy elderly in the Detroit area showed a mean zinc intake of 9.06 mg/day (12). Serum zinc levels in that study were comparable in young and older adults, but cellular levels (granulocytes and lymphocytes) were significantly lower in older adults. Selenium, a component of glutathione peroxidase, can have significant effects on immune function. Selenium deficiency is common in some parts of the world (parts of Asia and New Zealand) where the soil lacks selenium. In the United States selenium deficiency is rare, and although some studies suggested it may be present in elderly nursing facility residents or hospitalized patients receiving chronic tube feedings, currently available tube feeding formulations almost always contain selenium in sufficient quantities.

## Clinical Manifestations

There are several major risk factors for malnutrition in the elderly that may serve as clinical clues to the diagnosis. Poverty, social isolation, dependence or disability, chronic/multiple medications, and dental disorders all increase the risk of malnutrition in elderly adults. Many comorbidities are also risk factors (e.g., depression, stroke, congestive heart failure) and have specific symptoms and signs associated with the underlying disorder. Clinical clues of global undernutrition in elderly patients include: low body weight, muscle wasting, sparse/thinning hair, flaking dermatitis, cheilosis/angular stomatitis, poor wound healing, and peripheral edema. Specific symptoms, signs, and laboratory abnormalities associated with micronutrient deficiency are shown in Table 1.

## Diagnostic Tests

There are several office assessments of nutritional status that have been validated in elderly adults and thoroughly reviewed elsewhere (13). That extensive reference includes nomograms, chart forms, drug/nutrient interaction checklists, and

nutrition-screening protocols ranging from simple waiting room questionnaires to detailed anthropometric measures and laboratory assessments. One helpful screen is to simply assess weight and height and calculate body mass index (BMI; weight in kg/(height in cm)<sup>2</sup>). Older adults who experience  $\geq 5\%$  loss of body weight in 1 month, a body weight  $\geq 20\%$  below ideal body weight or a BMI  $> 27$  or  $< 22$  should have a more thorough assessment of nutritional status.

## **Nutritional Therapy for Prevention of Infection**

Despite strong evidence that malnutrition is common in the elderly and associated with poor immune function, there are very few studies that have shown nutritional support can improve clinical outcomes in this population. These studies are very difficult to perform, rarely done in hospitalized patients or nursing facility residents, and require large sample sizes to be powered for statistical significance for clinical end-points, and, thus, usually employ surrogate laboratory markers.

### ***Multivitamin/Mineral Supplementation to Enhance Immune Responses and Prevent Infection***

Several recent, very thorough reviews have been published regarding nutritional supplements on immune markers, infection risk and overall outcomes with regard to protein/calorie supplements (14) and multivitamin/mineral (MV/M) supplements (4, 15). General concepts contained within these reviews, specific pivotal trials, and clinical trials published since these reviews are highlighted below. One important note regarding these studies; earlier reviews on this topic have been heavily influenced by specific studies by the Chandra group in 1992 and 2002 demonstrating reductions in infectious illness and antibiotic use in studies of MV/M supplementation in Canadian seniors. Studies by this author may well have been fraudulent (16, 17) and are no longer utilized in most meta-analyses (4) and authoritative reviews; thus, the comments below exclude the data/conclusions from Chandra's studies.

Multivitamin/mineral supplements have been given in a variety of study designs. Most studies report enhancement of at least some surrogate markers (e.g., delayed-type hypersensitivity (DTH) responses, cytokine production). Recent meta-analysis of MV/M supplements to reduce infection in older adults (age 65 years and older) (4, 15) showed no significant benefit regardless of outcome studied (number of episodes of infection or number of individuals with at least one infection). The meta-analyses examined both community and long-term care studies and examined well-nourished and undernourished subjects. In a subgroup analysis, those that were undernourished at baseline and received supplementation for  $\geq 6$  months appeared to derive benefit (4). This outcome was primarily influenced by studies of Girodon and colleagues (18, 19). One study by this group in institutionalized

elderly utilizing a MV/M supplement showed decreased infection rates over a 2-year supplementation trial (18). In that study, nursing facility residents were randomly assigned to receive daily placebo, trace elements (20 mg zinc + 100 µg selenium), vitamins (120 mg vitamin C, 6 mg β-carotene, and 15 mg vitamin E), or both vitamins and trace elements. There were no immunologic studies performed, but the mean number of infections (respiratory and urinary tract infections were counted) was reduced in both groups taking trace elements vs placebo. Interestingly, the trace element group alone had the lowest rate of infection, and the vitamin + trace element group had similar rates of infection as the vitamin alone group. Importantly, this was a small study with four groups making it difficult to draw firm conclusions.

The second study by these authors (19) was much larger and randomized 725 long-term care facility residents in 25 facilities in a factorial design to receive trace elements (zinc 20 mg + selenium 100 mg), three vitamins (C 120 mg, E 15 mg and β-carotene 6 mg (=1,000 retinol equivalents)), both or neither for 2 years. Mortality was high in all four groups (~30%) and not different between groups, but this high mortality rate reduced the number of subjects with complete follow-up. There was no effect on delayed-type hypersensitivity responses, but a greater proportion of subjects in the trace element groups (vitamins + trace elements or trace elements alone) had protective antibody titers after influenza vaccination ( $p < 0.05$ ). Surprisingly, vitamins alone appeared to have had a negative effect on antibody titers ( $p < 0.05$ ). There was no effect on urogenital tract infections, but a trend toward reduced incidence of respiratory tract infections ( $p = 0.06$ ), again in both trace element groups, but not in those receiving vitamins alone.

A third randomized trial of MV/M supplementation in long-term care residents was published after the meta-analyses discussed above. That study by Lui and colleagues (20) was also a large, multicenter study enrolling 763 subjects at 21 sites over 18 months with the primary outcome of infections/subject and secondary outcomes of antibiotic use and hospitalization rates. The study demonstrated a borderline effect of MV/M supplementation on number of infections (OR = 0.77; 95% CI, 0.54–1.1) after controlling for other risk factors. Dementia was a particularly important predictor of infection risk and when those subjects without dementia were analyzed separately post hoc, the MV/M supplement was associated with a reduced risk of infection (OR = 0.81; 95% CI 0.66–0.99). The number of antibiotic courses and number of days on antibiotics were lower in the MV/M supplemented group ( $p = 0.05$  and  $p < 0.001$ , respectively), but MV/M use did not remain significant in a multivariate model. There was no significant effect on hospitalization.

Thus, it appears MV/M supplementation is of little value in well nourished older adults in the community (4, 21), but may reduce the risk of infection and antibiotic use in older nursing home residents, many of whom are malnourished at baseline. This conclusion is based on several multicenter trials that showed similar trends of borderline statistical significance (18–20). Large, randomized, well designed trials are needed to definitively address this issue.

### ***Zinc Supplementation Studies***

Zinc deficiency is common in older adults (Table 1) and low serum levels are associated with an increased antibiotic use and risk of pneumonia in nursing home residents (22). Studies in older adults have given several forms of zinc that range in dose from 15 mg/day of zinc acetate to 220 mg of zinc sulfate twice a day. Often zinc was administered with other single vitamins or a multivitamin supplement. Most demonstrated enhanced DTH responses, and many show enhanced lymphocyte numbers and function of NK cells, but no benefit for boosting humoral immune responses. Only the nursing home studies of Girodon (18, 19) described in the section “Multivitamin/Mineral Supplementation to Enhance Immune Responses and Prevent Infection” demonstrated significance with regard to clinical infection endpoints.

### ***Vitamin E Supplementation Studies***

Vitamin E, an antioxidant vitamin that has been touted as a preventive measure for many human conditions including heart disease and cancer, has also been extensively studied in the elderly as a booster of immune responses. It is not clear how vitamin E augments immune responses, perhaps via altering cytokine generation from T-cells or macrophages, or enhancing the immunologic synapse between antigen presenting cells and T cells (see (23) for review of mechanisms and major clinical trials of vitamin E supplementation in older adults). Vitamin E supplementation has resulted in improved DTH responses in elderly subjects with doses as low as 60 mg/day, and enhancement of primary immunization responses at doses of 200–800 mg/day. Several randomized studies of vitamin E supplementation examining clinical infection outcomes have been reported (reviewed in (23)) and conflicting data have emerged. No effect was shown in some studies, a borderline effect in others, and a significantly reduced risk of infection in others. Similar to MV/M supplementation trials, the greatest effect appears to be in residents of long-term care. In a randomized, placebo-controlled trial of 617 older adult long-term care residents in 33 facilities, vitamin E supplementation (200 IU daily on top of MV/M supplement containing 50% of USRDA recommended amount of all micronutrients provided to all subjects) was associated with a reduced risk of respiratory infection – common colds were reduced, but there was no effect on lower respiratory tract infection or antibiotic use (24).

### ***β-Carotene and Vitamin A***

Vitamin A is essential for proper immune function, but long-term supplementation can lead to hepatotoxicity. The vitamin A precursor, β-carotene, is not associated with liver toxicity and therefore is often used in supplementation trials. β-carotene

can enhance natural killer cell activity in elderly men over very prolonged follow-up (up to 12 years). However, no trial has demonstrated significant clinical benefit for reducing infection risk except when given as part of a MV/M supplement as described above.

### ***Vitamin D***

Vitamin D is among the most prevalent of nutritional deficiencies in older adults and supplementation is frequently provided for bone health and other benefits. Vitamin D is a markedly immunomodulatory compound as well with recent data suggesting it may be particularly important in immunity vs tuberculosis. There is only one large scale trial of vitamin D supplementation in older adults examining infectious outcomes and it is reported in brief form (25). No significant benefit was noted with regard to self-reported infection or antibiotic use.

### ***Cautions Regarding Nutritional Supplementation***

The public often regards vitamin therapy with the notion that if “some is good, more is better,” and assumes that nutritional products are not likely to do harm. Unfortunately, this is not always true, and caution should be exercised in recommending vitamin therapy in the absence of clear data to support its use. Large clinical trials and case-control studies have shown an increased risk of lung cancer and pneumonia in smokers receiving vitamin A or  $\beta$ -carotene, and an increased risk of hip and other fractures in those taking vitamin A supplements or with high serum levels of retinol. Further, vitamin E supplementation has been studied extensively in tens of thousands of subjects. A meta-analysis of these studies (26) demonstrated *increased* overall mortality with vitamin E supplementation  $\geq 400$  IU daily; the number needed to harm was only 257 (i.e., one excess death from treating 257 subjects). Many of these trials were in subjects at increased risk for cancer, heart disease and other chronic ailments and may overestimate the risk. However, the examples of unexpected toxicity in  $\beta$ -carotene and vitamin E trials certainly suggests one should exercise caution in providing nutritional supplements at doses above those demonstrated to be effective in clinical trials.

### **Nutritional Therapy During Established Infection**

Nutritional therapy has been employed in a large number of studies for many serious illnesses, but few have specifically focused on elderly subjects with infectious diseases. However, zinc supplementation has been suggested to be beneficial for

wound healing, especially for venous stasis ulcers, a common condition in the elderly and there are a significant number of trials. A recent meta-analysis (27) suggests that zinc supplementation, if helpful at all, is only likely to be of value in those patients with low serum zinc at the initiation of therapy. The appropriate dose and duration are not known, but in most studies 200–220 mg or zinc sulfate three times a day was given as the therapeutic regimen.

## **Nutritional Therapy During Convalescence After Infection**

Data from surgical patients suggest that the nutritional demands of the elderly remain during the period of convalescence with weight loss continuing for up to 8 weeks after hospital discharge. Few studies of sufficient power and appropriate design have been performed in the elderly that examine the influence of nutritional supplements on the risk of infectious diseases following other serious illness. Community-acquired pneumonia (CAP) is a common serious illness in the elderly and a study from Spain (28) suggests that up to 85% of elderly patients with CAP are malnourished at the time of admission (vs 53% of age/gender-matched controls admitted for other reasons in that study). Woo and co-workers (29) studied the effects of nutritional supplementation during convalescence from CAP in a group of elderly patients in Hong Kong. Most of these patients were not institutionalized but lived in the community with spouses or family. Patients were randomly assigned to receive 500 mL daily of a commercially available supplement (Ensure®) or no supplement for 1 month following discharge. As expected, several nutritional variables showed greater improvement in the supplemented group than in the nonsupplemented group. In addition, supplemented elderly were more likely to be physically active and had a higher functional status and less difficulty sleeping during follow-up visits (up to 3 months) than nonsupplemented elderly. The study was not powered to detect differences in survival or recurrent infection, and did not perform any measures of immune function. Another recent study (30) showed that 400 mL of an oral nutritional supplement for 6 weeks during and after hospitalization reduced non-elective readmissions in older adults (hazard ratio = 0.68; 95% CI 0.49–0.94), though infections were not a specific endpoint nor identified as a cause for readmission.

## **Conclusions and Recommendations**

Older adults are a population at special risk for malnutrition that may lead to increased risk of infection. Global malnutrition is particularly prevalent in hospitalized elderly and may become worse during the hospitalization. Reversible causes of malnutrition such as depression, dental disorders, poorly controlled diabetes, and medication-induced anorexia are common in elderly outpatients and undertreated. Among micronutrients, deficiencies of vitamins A, B<sub>12</sub>, and E and the trace elements zinc and selenium appear to be most prevalent and of greatest importance for immune function

in elderly subjects. Based on available data it is difficult to recommend any specific supplement to older adults who are well nourished living the community. The strongest data supporting supplementation appear to be for MV/M supplements in residents of long-term care to reduce the risk of respiratory tract infection and perhaps antibiotic use. Vitamin E at a dose not to exceed 200 IU daily may reduce the risk of upper respiratory tract infection in residents of long-term care as well. Specific replacement therapy should be provided for those individuals with documented deficiencies of other micronutrients (e.g., vitamin B<sub>12</sub>), but specific data regarding protective efficacy for infection is lacking. Commercially available nutritional supplements may be of benefit in hospitalized elderly and during convalescence from serious infectious illnesses such as pneumonia. Future studies should be of sufficient size to achieve statistical significance for clinically meaningful endpoints.

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# Sexually Transmitted Diseases

Helene Calvet

## Key Points

- Many older adults are sexually active and may be engaging in activities that put them at risk for STDs or HIV, so obtaining a sexual history from older adults is important for assessing risk.
- CNS syphilis can be difficult to diagnose; test for it in patients with neurologic findings and a positive syphilis serology.
- Gonorrhea and *Chlamydia* are uncommon among older adults, but herpes seroprevalence is higher in older adults than in younger age groups.
- Vaginal complaints in older women are more likely to be caused by normal physiologic changes (atrophic vaginitis) than due to STDs.
- HIV/AIDS is an increasing problem in those over age 50; routine screening is now recommended up to age 64.

## Introduction

In the United States, sexually transmitted diseases (STDs) are not perceived by most healthcare practitioners as a problem for older adults (over age 50). In fact, many practitioners do not view older adults as even being sexually active, much less at risk for STDs. Aging, intercurrent illnesses, and psychosocial factors often have a significant impact upon sexual function or the enjoyment of sex in the elderly. Psychosocial factors such as attitudes toward sexual behavior, reaction to physiologic changes or illness, performance anxiety, loss of partner, or loss of privacy can

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contribute to sexual dysfunction in both men and women. Aging women may experience a number of physiologic and anatomic changes due to the loss of estrogen, such as shortening and narrowing of the vaginal vault, thinning of the vaginal mucosa, and reduction or loss in vaginal lubrication (1, 2). These vaginal changes can predispose postmenopausal women to more frequent vaginal infections and atrophic vaginitis. In addition to these physiologic changes, medical conditions can contribute to dyspareunia, which is reported in up to two-thirds of postmenopausal women (1, 2). Physiologic changes in men cause decreased levels of testosterone, which can lead to the need for more stimulation to achieve or maintain an erection, rapid penile detumescence, and a prolonged refractory period (1). Erectile dysfunction is estimated to affect 10% of all men in the United States, with higher rates in those over age 40 and in those with medical conditions such as diabetes mellitus. Lindau et al., reported on the survey of U.S. adults aged 57–85, and among the men interviewed, 37% experienced erectile dysfunction and 14% reported using medications to supplement sexual function (3). There are numerous causes of erectile dysfunction, including medical illnesses, medications, normal physiologic changes and psychosocial factors.

Despite the many medical and psychosocial factors possibly preventing sexual activity in the elderly, multiple studies have shown that many older Americans still do engage in sexual activity. Lindau's survey found that 73% and 53% of those aged 57–64 and 65–74, respectively, reported sexual activity. That proportion drops to 26% among those aged 75–85 (3). It is unclear how many of those not engaging in sexual activity are celibate by choice or are affected by health status or by partner availability. With the current extent of sexual activity in the older age groups, safe sexual practices are important for STD and human immunodeficiency virus (HIV) prevention; however, few actually engage in safe sexual practices. Stall and Catania (4) found in a survey of over 2,000 Americans, aged 50 and older living in large metropolitan areas, that 11.7% reported at least one risk factor for HIV (multiple sexual partners, high-risk sexual partner, transfusion between 1978 and 1984, or injection drug use). Among those stating at least one risk factor for HIV, 73% were sexually active; 83% of these never used condoms. Men in this age group are less likely than their younger counterparts to use condoms because their partners, in general, are past child-bearing age. Older women may not view themselves as being at risk for STDs because they are postmenopausal, and STD risk is often linked to pregnancy risk (5). Also, older sexually active men may have multiple partners available due to the preponderance of widowed females who may be interested in maintaining sexual activity.

The lack of safe sexual practices in older adults and the changes in vaginal physiology in older women put them at risk for STDs and HIV. Although STDs are not frequently diagnosed in older adults, acquired immunodeficiency syndrome (AIDS) in older adults is not insignificant, with the over-50 age group accounting for 28% of the estimated numbers of persons living with AIDS in the United States in 2005 (6). People living with HIV/AIDS now have many more options for effective therapy and are living much longer, so the number of cases of HIV/AIDS in adults over age 50 is likely to continue to increase. Therefore, physicians need to ask older adults about HIV risk factors, and make a sexual history part of their routine

history-taking in older adults. However, discussions regarding sexual history do not appear to be taking place often. In Lindau's survey (3), only 38% of men and 22% of women reported ever having discussed sex with a physician since age 50. There are numerous barriers that may prevent either a clinician or a patient from discussing sexual issues, but in order to allow patients to discuss their concerns and to adequately assess risk for HIV and STDs, clinicians should start with several simple questions, examples of these questions are outlined in Table 1.

**Table 1** Sample questions for sexual history taking

Subject	Sample question(s)	Actions
Introduction/Opening	I'd like to ask you some questions about your sexual health. I ask all of my patients, regardless of age, these questions because they are just as important as other questions about your health. Everything we discuss is strictly confidential, and you do not have to answer any question you are not comfortable answering	HIV testing is recommended for all aged 64 and under; offer HIV testing if never tested (or if tested in the past and interim risk factors), regardless of their willingness to discuss sexual history
Sexual activity	Are you sexually active? <i>or</i> Do you have sex?	If answer is no, stop further questioning about sexual practices, but consider further questions about concerns about sexual functioning or barriers to sexual activity
Partners (gender and number)	Do you have sex with men, women or both? <i>and</i> How many partners have you had in the last year?	If male–male sexual activity, screen for HIV and syphilis annually
Practices	Tell me about your sexual practices <i>or</i> Do you have vaginal, anal or oral sex?	If male–male sexual activity, consider screening for rectal gonorrhoea if practicing receptive anal intercourse, and pharyngeal gonorrhoea if practicing receptive oral intercourse
Prevention	What are you doing to protect yourself from STDs and HIV? <i>or</i> Do you use condoms all of the time, some of the time, or never? (ask for each specific type of sexual activity)	If practicing risky activities, educate on importance of condom use for protection against STDs and HIV; discuss beliefs about and barriers to safer sex practices. Consider gonorrhoea and <i>Chlamydia</i> screening in patients with multiple unprotected contacts
Closing	Is there anything else about your sexual health you would like to discuss today?	

*HIV* human immunodeficiency virus, *STDs* sexually transmitted diseases

This chapter covers brief descriptions of the clinical presentations of selected STDs, new advances in the diagnosis of STDs, and epidemiologic trends of STDs in older adults. Also, highlighted will be the latest recommendations for management of STD's from the 2006 STD Treatment Guidelines (7) from the Centers for Disease Control and Prevention (CDC). The topic of HIV/AIDS is discussed completely in a separate chapter (see chapter "Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome"), and thus it will not be further discussed here.

## Syphilis

Nationwide statistics for syphilis are most important for early syphilis (primary and secondary) because these represent the recently acquired (incident) cases and the cases that are most infectious. Although the rate of primary and secondary syphilis declined substantially between 1990 and 2000, leading to the lowest reported rate of early syphilis since 1941, the rates increased again between 2001 and 2006. Much of this increase has been due to syphilis among men who have sex with men (MSM); in 2004, they accounted for an estimated 62% of the early syphilis cases (8). Although the highest rates of early syphilis are among younger men, between 2000 and 2006, the rate in men aged 45–64 has more than doubled (8), so clinicians should be aware of the epidemiologic changes in syphilis, and they should consider screening older MSMs. Regardless of age group, early syphilis is highly infectious, with an estimated 30% chance of acquiring infection after a single sexual contact (9). In older women, the risk may be higher due to vaginal thinning in the postmenopausal state, leading to more abrasions during sexual intercourse. The clinical presentation of syphilis is beyond the scope of this brief review but has been described in a recent review (9). Early syphilis should be considered in the differential diagnosis of any new genital ulceration, especially if the ulceration is painless, or for unexplained skin rash in a patient with high-risk sexual activity, especially MSMs.

The diagnosis of syphilis in the elderly may be challenging for several reasons. First, in the elderly, the prevalence of false-positive nontreponemal serologies such as the rapid plasma reagin (RPR) or venereal disease research laboratory (VDRL) has increased. Prior to considering treatment in all age groups, it is necessary to confirm a positive nontreponemal test result with a treponemal-specific serology such as the *Treponema pallidum* particle agglutination (TP-PA) or fluorescent treponemal antibody absorbed (FTA-ABS). Second, in patients who have untreated syphilis for many years and are presenting with late complications, the RPR and VDRL may be negative, with only a positive treponemal serology as indication of infection. Therefore, the possibility of either false-positive or false-negative screening nontreponemal tests exist in the elderly. Finally, since the elderly have many intercurrent illnesses and are not perceived by medical providers as being sexually active or at risk for syphilis, symptoms or signs of syphilis may be

mistaken for other disease states such as a drug reaction, urinary tract infection, or benign perineal ulceration.

Whereas early syphilis is uncommon in the elderly, latent syphilis is a more frequently encountered problem. A nontreponemal syphilis serology is a routine test that is performed in the evaluation of dementia or a cerebrovascular accident, so a common dilemma is how to determine the significance of a positive result. If the confirmatory test is positive, then the clinician must decide whether the patient requires an evaluation for neurosyphilis. According to the 2006 Centers for Disease Control Prevention (CDC) STD Treatment Guidelines (7), cerebrospinal fluid (CSF) evaluation is recommended if the patient has any of the following: (1) neurologic or ophthalmic symptoms or signs suggestive of syphilis (such as uveitis, interstitial keratitis, cranial nerve palsies, cerebrovascular accident, or the psychological or behavioral changes suggestive of general paresis that can occur many years after infection), (2) suspected treatment failure, demonstrated by a failure to resolve mucocutaneous signs of primary or secondary syphilis or the lack of a fourfold drop in the RPR (or VDRL) titer in a timely fashion after treatment, (3) co-infection with HIV and syphilis of greater than 1 year duration, or (4) evidence of active tertiary syphilis (aortitis, gummas). If the patient undergoes a lumbar puncture, then the clinician must be aware of potential difficulties in interpretation of the CSF findings. There is no one test that is 100% sensitive for the diagnosis of neurosyphilis. In a patient with positive serum syphilis serology, if the CSF VDRL is positive (without significant contamination of the CSF with blood), most experts would agree that the patient has neurosyphilis. However, in patients with negative CSF VDRL, the clinician should consider treatment if there is any abnormality of the CSF such as a pleocytosis or elevated protein, even though these findings are not specific for neurosyphilis. It is important to recognize, however, that the protein level in the CSF may increase with age and other associated conditions, thus the interpretation of the CSF profile, with a slightly elevated protein level as the sole abnormal finding, may be difficult. Although the FTA-ABS is not a recommended test to perform on CSF because of problems with specificity, a negative CSF FTA-ABS suggests that neurosyphilis is unlikely. The many presentations of neurosyphilis and the difficulties in diagnosis are comprehensively reviewed elsewhere (10).

The recommended treatment of syphilis has not changed recently. Syphilis of less than 1 year duration (primary, secondary, and early latent) is treated with a single injection of benzathine penicillin (2.4 million units (MU) intramuscularly (i.m.)) and syphilis of more than 1 year duration (late latent and tertiary) is treated with weekly injections of intramuscularly administered benzathine penicillin (2.4 MU for 3 weeks). If the patient is late for a dose, then an interval of 10–14 days between doses may be acceptable before having to restart the course of therapy (7). The treatment of neurosyphilis is best accomplished with 18–24 MU of intravenous (i.v.) penicillin G for 10–14 days. An alternative regimen, which can be administered on an outpatient basis, is procaine penicillin (2.4 MU i.m. administered once a day) along with probenecid (500 mg orally four times a day) both for 10–14 days (7). Many experts recommend treating patients with neurosyphilis with an additional

two injections of 2.4 MU benzathine penicillin weekly immediately following the course of i.v. penicillin in order to achieve the same duration of therapy as would be given for tertiary syphilis.

## **Herpes Simplex Virus, Type II (HSV-2)**

Genital herpes simplex virus (HSV) infection is not a reportable disease; however, based on the serologic results of a random sampling of civilian adults examined as part of the National Health and Nutrition Examination Survey (NHANES) it is considered to be extremely common in the United States, with an estimated seroprevalence of 17% in adults in 1999–2004 (11). This seroprevalence is 19% lower than that found during 1988–1994, when the seroprevalence of HSV-2 was 22% among the adult population during NHANES III (12). Although the latest study limited the analysis to adults aged 49 and under, the prior study (NHANES III, 1988–1994) found that the prevalence of HSV-2 infection increased with increasing age, and independent predictors of HSV-2 serologic status were of the independent predictors of HSV-2 serologic status were if the patient was female gender, of the black race or Mexican-American ethnic background, of an older age, had less formal education, had an income below poverty level, and had greater number of lifetime sexual partners. Overall in NHANES III, those age 50 and over had age-adjusted prevalence of HSV-2, ranging from 24 to 28% (12). Therefore, HSV-2 infection is prevalent in older adults and should be considered in the differential diagnosis of a genital or perineal ulceration or rash, especially if it is resistant to usual local care measures.

The majority of people testing positive for antibodies to HSV-2 have subclinical, atypical, or asymptomatic disease, with the minority displaying the classic presentation of vesicular outbreaks. During NHANES III, only 2.6% of adults reported having ever had genital herpes, but almost 22% of those who did not report having herpes had type-specific antibody to HSV-2 (12). Studies estimate that 70–80% of patients testing positive for HSV-2 antibodies are not aware of the infection, but up to 50% of these individuals will give a history of atypical symptoms that may be due to HSV reactivations (13). Recurrences are common after newly acquired infection, with 38% having six or more recurrences and 20% having ten or more recurrences in the first year after acquiring the virus; however, the longer the time period from infection the less frequent the outbreaks tend to become (14). Immune suppression associated with aging or other concomitant morbid conditions in the elderly may lead to an increase in the frequency of recurrences or a recrudescence after many years of no clinically recognizable outbreaks. Atypical (non-ulcerative) presentations of HSV-2 may be more common than the classic vesiculating outbreak, so clinicians need to be aware of other genital symptomatology such as recurrent burning, itching, or irritation that may be due to HSV-2 recurrences.

The gold standard for diagnosis of HSV infection remains the viral culture. The overall sensitivity of culture is best in vesicular lesions but is lower in other lesions, estimated to be approximately 70% in ulcerative lesions and only 30% in

crusted lesions (14); therefore, a negative culture result does not exclude the diagnosis. Culture is also more sensitive in primary infection than recurrent disease. Antigen detection tests also lack sensitivity and do not distinguish between HSV-1 and HSV-2. Since many patients may not present with the classic vesicular lesions, culture or antigen tests may not be helpful in making the diagnosis of atypical HSV-2 infections. For these situations, new type-specific serologies are available. These type-specific serologies are superior to older, nonspecific serologies in that they can accurately differentiate between HSV-1 and HSV-2 infection. HerpeSelect® (Focus Diagnostics, Inc), CAPTIA™ HSV ELISA (Trinity Biotech USA), and biokitHSV-2 Rapid Test (biokit USA) are three commercially available type-specific herpes serologies that have >90% sensitivity and specificity (15). Clinicians should consider checking a HSV-2 serology for patients with undiagnosed, bothersome recurrent genital symptoms.

Three effective medications are available for the treatment of herpes (see Table 2 for doses and duration of treatment.) If an elderly patient experiences frequent recurrences (>6 per year), then chronic suppression should be considered. The need for continued suppressive therapy should be reevaluated after 1–2 years by a trial without suppressive medications. If recurrences are sporadic at that time, then sporadic treatment can be given. If recurrences are frequent again, then another year of suppression is indicated. HIV testing should be considered in the elderly patient experiencing frequent herpetic recurrences who has not recently acquired herpes, as frequent recurrences in long-term disease is unusual.

Counseling of older individuals with HSV genital infection should include information about the natural history, probability of recurrences, benefit of treatment, and chances for transmission. Transmission can occur in the absence of clinical symptoms or signs of an outbreak; in fact, most sexual transmission occurs

**Table 2** Treatment of genital herpes simplex-2<sup>a</sup>

Reason for treatment	Duration of therapy	Medications		
		Acyclovir	Famciclovir	Valacyclovir
First clinical episode	7–10 d	400 mg po tid	250 mg po tid	1 g po bid
Recurrent episodic	Varies	400 mg po tid or 800 mg po bid × 5 d, or 800 mg po tid × 2 d	125 mg po bid × 5 d or 1 g bid × 1 d	500 mg po bid × 3 d or 1 g po qd × 5 d
Recurrent suppression	1 year <sup>b</sup>	400 mg po bid	250 mg po bid	500 mg po qd <sup>c</sup> or 1 g po qd

*d* day, *po* orally, *qd* once daily, *bid* two times a day, *tid* three times a day

<sup>a</sup>For non-HIV infected; see STD Treatment Guidelines for doses recommended in HIV infection (7)

<sup>b</sup>Therapy longer than 1 year may be indicated if recurrences continue to occur frequently or if psychological adjustment to diagnosis poor

<sup>c</sup>Valacyclovir 500 mg qd dose less effective than other valacyclovir or acyclovir dosing regimens for very frequent recurrences (≥10 per year) (7)

due to asymptomatic shedding. Therefore, patients with genital herpes should be counseled to use condoms at all times to reduce the risk of transmitting the infection to a partner.

## Chlamydia

*Chlamydia trachomatis* infection is the most common reportable communicable disease in the United States and the numbers of infection continues to rise each year. Chlamydia is an infection predominantly of adolescents and young adults, with the highest rate of infection being in the 15–19 and 20–24 year age groups. The prevalence of infection drops off greatly after age 35, with adults over age 55 having very low incidence (<10/100,000 for those 55–64, and <3/100,000 for those 65 and older) (8). The reasons for the predilection of younger age groups to *Chlamydia* are both anatomical and behavioral. *Chlamydia* is an intracellular organism that infects only columnar epithelium, which is often present on the ectocervix of adolescent girls, thus very accessible to infection. In older women, however, the columnar epithelium is located in the endocervix, an anatomical area more difficult to infect. Patterns and rates of partner change also make adolescents and younger women more susceptible to *Chlamydia*. However, older men and women are not immune to the disease. As in men, *Chlamydia* can also infect the urethra in women, causing symptoms of urinary tract infection or urethral syndrome. *Chlamydia* should be considered as a cause for culture-negative urinary symptoms in the sexually active elderly population, especially if sexual partners are in younger age groups. Aside from urethritis, the other common clinical presentation is cervicitis, but the majority of those infected in younger age groups is asymptomatic and is diagnosed through routine screening. Due to the low prevalence, routine screening for *Chlamydia* is not recommended in older adults, but screening should be considered for women at high risk (multiple sex partners, no use of barrier methods).

The diagnosis of *Chlamydia* infections has been revolutionized by the commercial availability of the nucleic acid amplification tests (NAATs), which utilize such technologies as polymerase chain reaction (PCR), transcription-mediated amplification (TMA), and strand displacement amplification (SDA). All of these NAATs have been Food and Drug Administration (FDA) approved for testing on urine samples in both men and women, obviating the need for uncomfortable urethral swabs for men or pelvic examinations for women, but can also be performed on urethral or cervical samples. The specificity of all these tests is high (95–98%), and the sensitivities are the highest among all classes of *Chlamydia* testing technologies, ranging from 90% for PCR, 94–97% for TMA and 81–94% for SDA, depending on the anatomic source of the specimen (16). Treatment of *Chlamydia* can be accomplished with an oral single-dose of 1 g of azithromycin or with oral doxycycline (100 mg twice a day for 7 days) (7). Azithromycin achieves high concentrations in tissues, with therapeutic levels of drug persisting for 1 week; the single-dose therapy has been found to be as efficacious as the doxycycline regimen. Partner treatment is important to prevent recurrent infection.



## Gonorrhea

Gonorrhea (GC) is the second most common reportable disease in the United States. It causes clinical syndromes similar to *Chlamydia*, with urethritis and cervicitis being the most common clinical presentations. Rectal and pharyngeal infections are also possible but are usually asymptomatic. Unlike *Chlamydia*, GC may disseminate to cause arthritis and/or dermatitis. Whereas the national rates of gonorrhea decreased 74% between 1975 and 1997, rates plateaued thereafter and actually increased in 2005 and 2006. Like *Chlamydia*, GC is a disease mostly of adolescents and young adults, with highest rates in those aged 15–29 years old. Rates in older adults are low, and although overall reported cases of GC number about one-third that of *Chlamydia* cases, the rates of GC in men over age 45 tend to be almost two times higher than the rates of *Chlamydia* in the same age groups (8). There is no evidence that the presentation of gonococcal disease in the elderly is any different than in those younger, but like other STDs, the diagnosis may be delayed because it is not considered in the differential diagnosis. It is unclear if the elderly are more susceptible to disseminated GC than others, but there are many case reports of disseminated infection in older individuals in the literature.

The diagnostic test for gonococcal urethritis that is most inexpensive and can yield immediate results is the Gram stain, which is highly sensitive in men with symptomatic urethritis. In asymptomatic men and in women with cervical infection, however, the sensitivity of Gram staining is much lower, so the diagnostic tests preferred in these groups include culture, DNA hybridization, or the NAATs (PCR, TMA or SDA). NAATs can be used for urine, urethral, or cervical samples. All of these tests yield sensitivities greater than 90%, except in the case of female urine samples, for which PCR and SDA have lower sensitivities (65% and 85% respectively) (16). The treatment of uncomplicated genital gonorrhea infection has become more challenging, due to the increasing prevalence of quinolone-resistant GC and the unavailability of certain regimens. Quinolone resistance was first noted by CDC surveillance systems in the United States in 1991, but, until 1999, remained at very low and stable levels. Since that time, there has been a dramatic rise in the proportion of resistant isolates, which accounted for almost 14% of the total tested in 2006 through CDC surveillance (8), leading to the deletion of all quinolone regimens from the list of recommended regimens for the treatment of uncomplicated GC infections (17). Currently, the only medications recommended for use include a single IM dose of ceftriaxone, 125 mg, or a single oral dose of cefixime, 400 mg (currently not available in U.S.). Alternative regimens for treatment include one dose of spectinomycin (2 g IM) (currently not available in U.S.), or other single-dose intramuscular cephalosporin regimens (ceftizoxime 500 mg or cefotaxime 500 mg). Some evidence suggests that single-dose cefpodoxime 400 mg or cefuroxime axetil 1 g might be oral treatment alternatives but are not effective for pharyngeal infection. Azithromycin (2 g orally) is effective, but, due to the concern of possible resistance, it is not recommended; however, it is an option for a patient allergic to cephalosporins or penicillin. Concurrent treatment with doxycycline for *Chlamydia*

infection is recommended if empirical treatment is being administered, and partner treatment is important to avoid reinfection.

## Vaginitis

Vaginal complaints are a common reason for women of all ages to visit their physician, accounting for an estimated 4 million initial visits to physicians' offices in 2006 (8). Decreased estrogen production in the postmenopausal woman causes a number of changes in the vagina, which can lead to a variety of symptoms. The amount of glycogen in the epithelial cells diminishes, leading to a reduction in the lactobacilli population which, through its production of lactic acid and hydrogen peroxide, helps to protect the vagina from colonization with other bacteria. The resulting increase in pH facilitates colonization of the vagina with coliform bacteria, streptococci, and staphylococci. The lack of estrogen also leads to thinning of the vaginal mucosa, loss of rugae, and a progressive loss of elasticity and vascularity. The vaginal vault shortens and narrows and the vaginal introitus may also become contracted. Physical signs of vaginal atrophy include pale, smooth shiny mucosa. Such changes have been theorized to lead to an increased risk of HIV infection, and studies have shown that, in 27–65% of postmenopausal women, these changes can lead to dyspareunia, vaginal dryness, or soreness (2, 18). If atrophic vaginitis develops, signs of inflammation will also be present such as erythema, petechiae, friability, bleeding, or discharge, and symptoms may include pruritis or burning (19). It is important for the healthcare provider to recognize this condition not as an infection or STD but as a syndrome of hormone deficiency, as most women will respond to hormone replacement.

Bacterial vaginosis (BV) and candidiasis are not sexually transmitted infections, but may arise in older women because of the changes in the vaginal microflora that occur in the postmenopausal state. Because these conditions are not STDs, they are not discussed further here, but the reader is referred to the STD Treatment Guidelines for discussion on the diagnosis and treatment (7). Trichomoniasis, caused by *Trichomonas vaginalis*, is an STD, which in women can infect the vagina, cervix, urethra, or bladder. Trichomoniasis is not a reportable disease, so accurate data on the incidence of this infection in older women are not available. Common signs due to trichomoniasis include abnormal discharge, which is often discolored and/or frothy, vaginal erythema, and punctuate cervical hemorrhages. Symptoms include discharge, itching, or burning of the vagina or vulva, but occasionally women will present with predominantly urethral complaints such as frequency, urgency, or dysuria. Trichomoniasis, like other STDs, may also be carried asymptotically for long periods of time, and the host factors that allow the asymptomatic carriage have not been elucidated.

Trichomoniasis can be diagnosed by seeing motile trichomonads on a saline preparation of vaginal secretions, but this test is estimated to be only 60–70% sensitive (7). In some cases, the trichomonads may not be readily visualized, so the clinician should suspect the diagnosis if the wet mount has numerous WBCs,

the pH is elevated, and the “whiff” test (amine odor after addition of 10% potassium hydroxide to vaginal secretions) is mildly positive. Many physicians may not have the equipment or training to perform the wet mount of vaginal secretions, but several point-of-care tests (OSOM Trichomonas Rapid Test, Genzyme Diagnostics, and Affirm™ VP III, Becton Dickinson) have been FDA-approved for the diagnosis of trichomonas (7). Culture systems are also available. Trichomoniasis is treated with a single oral dose of either 2 g metronidazole or 2 g tinidazole (7), and due to the difficulty of diagnosing the infection in men, partner treatment is recommended.

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# Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome

Jason B. Kirk and Matthew Bidwell Goetz

## Key Points

- The prevalence of HIV infection is increasing among the elderly. Unfortunately, the diagnosis of HIV infection is frequently delayed in older patients, as some symptoms of HIV infection may be confused with other complications of aging.
- On average, from the time of initial infection, elderly patients progress more rapidly to AIDS and death than do younger patients.
- The immunological compromise of HIV infection (i.e., loss of CD4<sup>+</sup> cells) results in opportunistic infections (e.g., *Pneumocystis jiroveci* pneumonia) and malignancies (e.g., non-Hodgkin's lymphoma). In addition, recent evidence indicates that HIV infection is associated with increased rates of mortality in persons with relatively intact CD4<sup>+</sup> cell counts (i.e., >350 CD4<sup>+</sup> cells/ $\mu$ L).
- The presence of comorbidities including liver, cardiac, and renal disease is more likely to complicate the course of HIV infection in older than in younger persons.
- Although older HIV-infected patients tend to be more adherent to antiretroviral therapy than are younger patients and often have decreased rates of virological failure, older HIV-infected patients frequently have slower and less complete restoration of CD4<sup>+</sup> cell counts than do younger patients.

## Epidemiology and Clinical Relevance

### *Epidemiology*

Human immunodeficiency virus (HIV)-infected patients are considered to be elderly when they are over the age of 50 (1). Using this threshold, the number of

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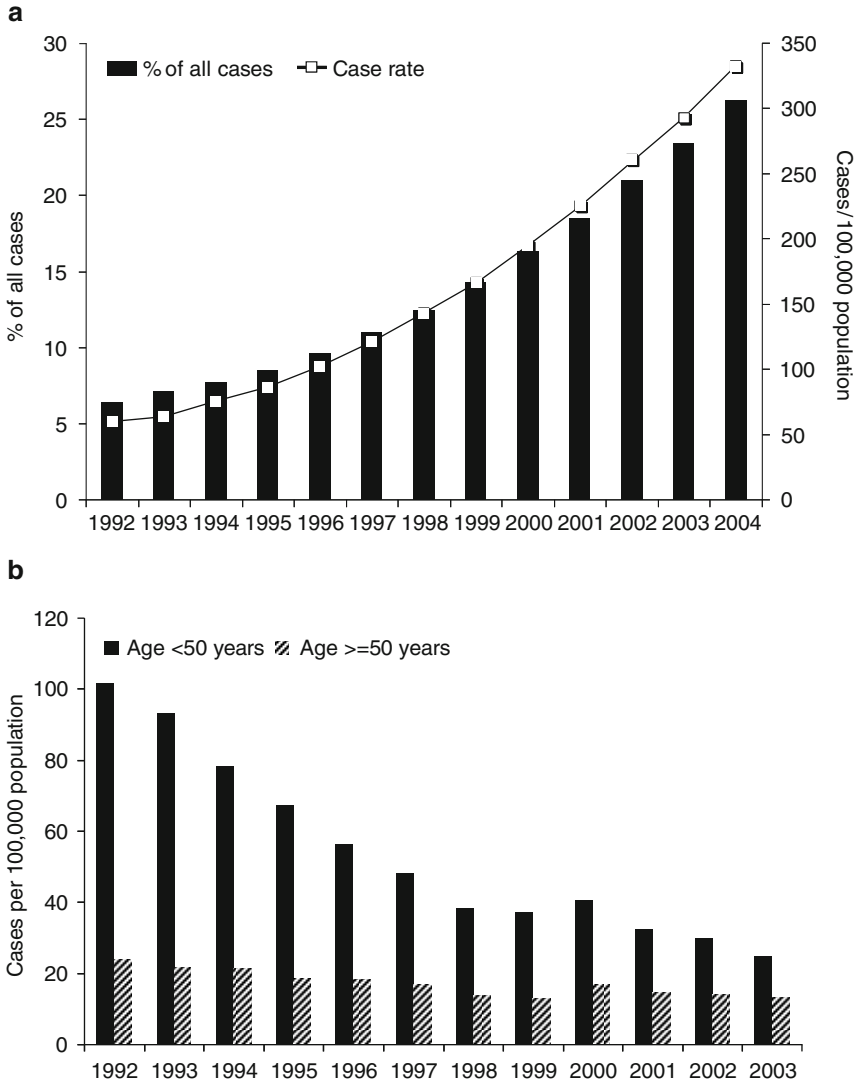
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HIV-infected patients in the United States has greatly increased since 1996 when Combination Antiretroviral Therapy (CART, or sometimes also referred to as Highly Active Antiretroviral Therapy or HAART), became available. With the advent of CART, HIV infection ceased to be a nearly inexorably fatal illness and has since become a treatable, chronic disease that can be managed like other illnesses such as diabetes and cardiovascular disease. Consequently, many HIV-infected patients who were infected in youth are now living into their 50s, 60s, and beyond. The impact of CART is evident, as in 1982 only 7.5% of patients with diagnoses of advanced HIV infection (i.e., patients with the acquired immunodeficiency syndrome (AIDS)) in the United States were  $\geq 50$  years of age; in 2005 these individuals accounted for 15% of new diagnoses of HIV infection, 24% of persons living with HIV infection, and 35% of all deaths of HIV-infected persons (2).

Particularly robust data regarding the impact of HIV in the elderly is available from New Jersey, where data have been collected not only on persons with AIDS, but also on all persons found to be in the earlier stages of HIV infection. In this state, which has the fifth highest number of AIDS cases in the United States, there were 1,048 (60/100,000) persons age  $\geq 50$  living with HIV infection in 1992 vs. 8,630 (332/100,000) in 2004. During this period, persons  $\geq 50$  years of age, most of whom were diagnosed earlier in life, increased from 6.4 to 26.2% of all people living with HIV infection. In addition, the proportion of older persons with new diagnoses of HIV infection increased from 6.4% of all diagnoses in 1992 to 17.9% in 2004 (see Fig. 1). Finally, whereas the rate of newly diagnosed cases of HIV infection declined by 70% in those younger than 50 (from 102/100,000 to 25/100,000 population), a lesser 46% decline was observed in those aged  $\geq 50$  (from 24/100,000 to 13/100,000 population) (3).

More so than young people, HIV, in the United States, disproportionately impacts elderly individuals who belong to ethnic and racial minorities. In 2005, the rates of diagnosed HIV infection among persons 50 and older were 12 times higher in blacks and five times higher in Hispanics than they were in whites (4). In comparison, among persons younger than 50, this rate was seven times higher in blacks and three times higher in Hispanics. In contrast to the 1980s when most infections in older patients were due to the receipt of contaminated blood products, in 2005, 53% of elderly HIV-infected men had engaged in sexual activity with men while 19% of HIV-infected elderly persons were injection drug users. Again, the demography of HIV in the elderly differs from that of younger patients among whom 69% of all HIV-infected males were men who had sex with other men; injection drug users accounted for 11% of cases (4).

Unfortunately, despite the time between infection and the development of AIDS symptoms taking as long as 10–20 years to emerge, and ample evidence of ongoing sexual activity (5) and infrequent condom use (1) in the elderly, healthcare providers often avoid discussing risk factors for HIV infection or offering testing to this population. Moreover, practitioners often fail to recognize the clinical manifestations of advanced HIV infection in the elderly, which more often presents as HIV encephalopathy and HIV wasting syndrome, conditions that mimic many other illnesses in the elderly (1, 6).



**Fig. 1** (a) Rate of HIV Infection and AIDS (HIV infection) in persons 50 years old and greater in New Jersey. (b) Rate of new HIV infection diagnoses in persons less than 50 and 50 years old and greater at the time of diagnosis in New Jersey

As a consequence of delays, when finally diagnosed, HIV-infected elderly patients generally have more advanced disease than do younger patients (1, 4, 7). In 2005, 53% of older HIV-infected persons in the United States vs. 37% of younger persons developed AIDS within 12 months of their diagnosis of being infected with HIV (4). Furthermore, although older persons are just as likely as younger persons to receive timely therapy for community-acquired pneumonia (8),

when hospitalized, for what is ultimately found to be *P. jiroveci* (previously called *P. carinii* f.sp. *hominis pneumonia* (PCP) (one of the most common AIDS-defining opportunistic infections) older persons are less likely to be evaluated for HIV infection, less likely to receive timely PCP-specific therapy, and less likely to survive their hospitalization (8).

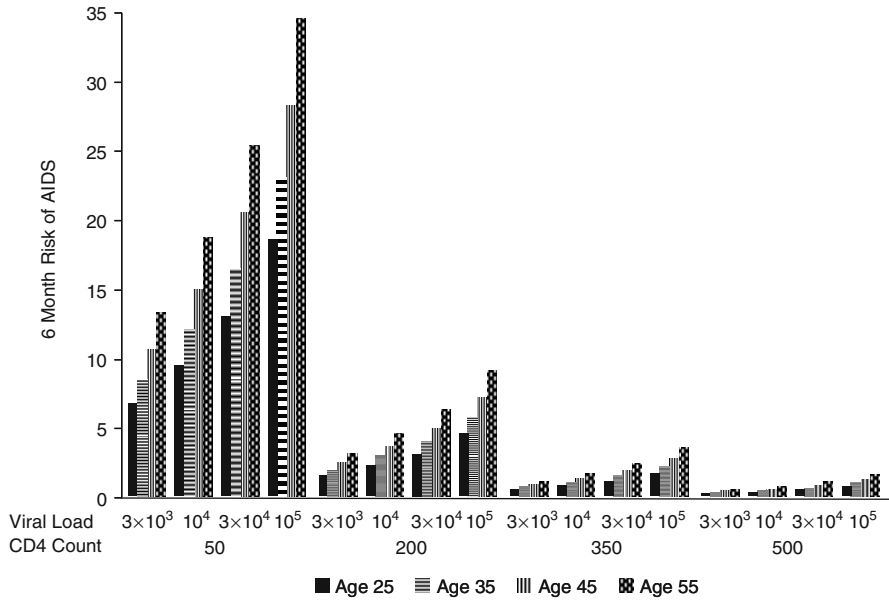
### *Clinical Course*

The clinical course of HIV infection can be categorized as consisting of three phases, namely seroconversion, clinical latency, and development of AIDS. Within 2–4 weeks after infection, approximately two-thirds of acutely infected individuals develop a mononucleosis-like seroconversion reaction, which is characterized by fever, mucosal ulceration, lymphadenopathy, rash, and occasionally aseptic meningitis and other neurological abnormalities. After several weeks, these findings spontaneously resolve and infected individuals enter a period of clinical latency wherein symptoms and signs of HIV infection are largely absent. However, despite the absence of clinical findings, persistent HIV replication, which may result in the production of up to 10 billion virions per day, leads to destruction of CD4<sup>+</sup> cells and ultimately to the development of opportunistic infections, malignancies, and other complications of HIV infection. Consequently, in the absence of effective intervention with antiretroviral therapy, during the 10-year period following infection, approximately 60% of patients develop an HIV-related opportunistic infection or malignancy. Disease progression is largely determined by the rate of CD4<sup>+</sup> loss, which on average ranges from approximately 20–80 cells/ $\mu$ L/year (9).

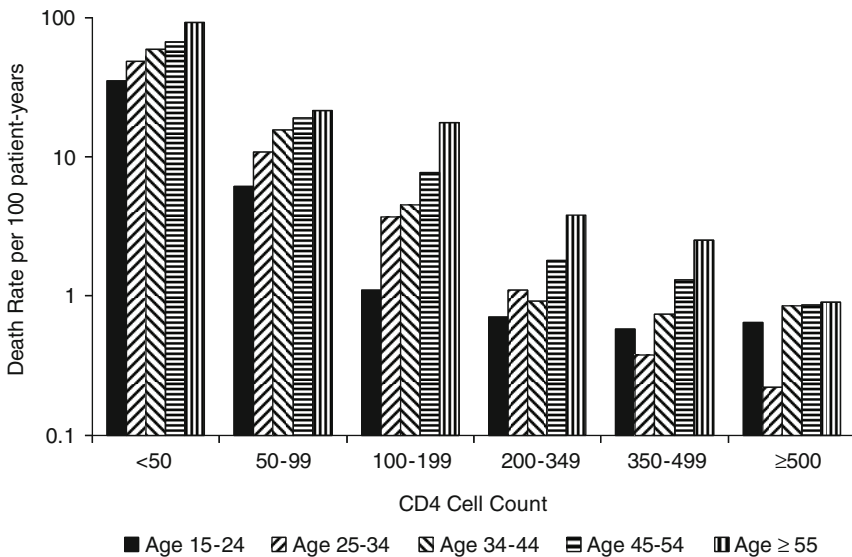
The relationship between patient age and the natural history of HIV infection in untreated (or minimally treated) patients has been best demonstrated in studies of the pre-CART illness course in more than 13,000 patients with known dates of HIV seroconversion. The CASCADE investigators have demonstrated that the median survival of HIV-infected patients was 12.5 years for those aged 14–24 years at the time of infection vs. 7.9 years for those aged 45–54 years and that the time to development of AIDS was 11.1 and 7.7 years, respectively (10). The rates of disease progression showed that there was a 1.47 fold increased risk of death and 1.32 fold increased risk of developing AIDS for every 10 years of increased age (10); this increased risk persisted after accounting for the baseline CD4<sup>+</sup> count and viral load (11) (see Figs. 2 and 3). Finally, the rate of CD4<sup>+</sup> cell decline was age related. After 5 years of infection, persons who were over the age of 40 at the time of seroconversion had 90 fewer CD4<sup>+</sup> cells/ $\mu$ L than did persons who were 16–20 years old at the time of HIV infection (12).

The complications of HIV infection are primarily related to immune failure. The severity of immune compromise is denoted by the loss of CD4<sup>+</sup> cells with AIDS-related diagnoses being uncommon until the CD4<sup>+</sup> count falls below 200 cells/ $\mu$ L. The mechanisms by which HIV infection induces the depletion of CD4<sup>+</sup> cells are multifactorial. Relevant to elderly HIV-infected patients is that although the inciting events differ, immune failure is likely to be related to chronic immune activation in





**Fig. 2** The figure displays the projected rates of progression to a clinical AIDS diagnosis over the next 6-month period after the indicated viral load (HIV-1 RNA copies/mL) and CD4+ cell counts (cells/ $\mu$ L) for persons aged 25, 35, 45 and 55. Data are from persons followed prospectively from the time of HIV seroconversion in the CASCADE cohort. Patients either received monotherapy or duotherapy with nucleoside reverse transcriptase inhibitors (prior to 1995) or were treatment naïve



**Fig. 3** Observed rates of death in non-injection drug users vs. the most recent CD4 count. Data are from persons followed prospectively from the time of HIV seroconversion in the CASCADE cohort. Patients either received monotherapy or duotherapy with nucleoside reverse transcriptase inhibitors (prior to 1995) or were treatment naïve

both HIV-infected persons and the elderly (13). Furthermore, much of the perturbation of the immune system in HIV-infected patients resembles the immunological changes seen with aging. Inversion of the normal CD4<sup>+</sup>/CD8<sup>+</sup> ratio, reduced numbers of naïve CD4<sup>+</sup> cells, changes in cytokine profiles (decreased IL-2 production and increased IFN- $\gamma$ ), telomere shortening in CD8<sup>+</sup> cells, decreased T-cell proliferation, and increases in late differentiated CD4<sup>+</sup> and CD8<sup>+</sup> cells are observed in both HIV-infected persons and the non-HIV-infected elderly (14). Finally, in both HIV-infected patients and the elderly the presence of an inverted CD4/CD8 ratio and decreased proliferative capacity of T cells is predictive of mortality. Thus, the additive effects of HIV and aging on immune activation may accelerate the progression of immunosenescence and immune failure in older HIV-infected patients.

## Clinical Manifestations

There are no unique manifestations of HIV disease in the elderly. However, HIV-associated wasting (weight loss) and HIV-associated dementia (HAD) are more frequently seen in older than in younger individuals (1, 6). Analyses of the Hawaii Aging with HIV Cohort study demonstrated the presence of HAD in 25% of HIV-infected patients over the age of 50 vs. 14% of HIV-infected persons aged 20–39 (6). After adjusting for receipt of CART, the viral load and CD4<sup>+</sup> count, older patients remained three times more likely to have HAD (6). The clinical features of HAD include problems with short-term memory, cognitive slowing, and poor attention, resulting in complaints such as difficulty reading and apathy. Findings may be subtle or indicative of advanced dementia with global cognitive dysfunction. Other HIV-related neurological complications include motor dysfunctions, manifest by difficulty walking, with stumbling, incoordination, and impaired dexterity.

Otherwise, the key distinguishing clinical feature of HIV infection in older persons is the presence of more comorbidities, including substance use and psychiatric disorders; these features are less prevalent in younger HIV-infected persons (15). There is no doubt that tobacco, recreational drug or alcohol use, and the normal consequences of aging contribute to the development of medical comorbidities in older HIV-infected persons. Furthermore, various antiretroviral agents are associated with lactic acidosis, peripheral neuropathy, diabetes mellitus, renal dysfunction, liver disease, and other comorbidities (9). However, a growing body of evidence indicates that HIV infection per se also contributes to the onset and severity of comorbid conditions (16, 17). Most noteworthy are findings in treatment-naïve HIV-infected patients with  $\geq 350$  CD4<sup>+</sup> cells/ $\mu$ L. Although AIDS-defining opportunistic infections and opportunistic neoplasms are rarely observed at this CD4<sup>+</sup> stratum, analyses of clinical cohorts still demonstrate an association of higher viral loads or lower CD4<sup>+</sup> cell counts (e.g., with 375 CD4<sup>+</sup> cells/ $\mu$ L as opposed to 500 CD4<sup>+</sup> cells/ $\mu$ L) with increased mortality in this setting (17). Similarly, the adjusted risk of having vascular, pulmonary, liver, or renal disease has been reported to be increased in HIV-infected persons with  $< 200$  CD4<sup>+</sup> cells/ $\mu$ L (15).

The mechanisms by which HIV infection may increase non-AIDS related mortality (i.e., mortality not due to opportunistic infections, opportunistic malignancies or other AIDS defining diagnoses) remain to be determined. However, it is of note that increased mortality due to non-AIDS defining conditions in HIV-infected patients may be related to disturbances in endothelial cell function and inflammatory cytokines, as indicated by increased D-dimer and IL-6 levels (18).

Analyses of cardiovascular mortality illustrate the complicated relationship between HIV infection, antiretroviral therapy, and the development of comorbidities. The SMART study, which had 5,472 participants, demonstrated that discontinuation of CART was associated with subsequent increased rates of cardiovascular disease and renal disease (19). In contrast, analyses of the D:A:D cohort of 23,437 HIV-infected patients found that HIV-infected persons treated with protease inhibitor-containing CART regimens had a significantly increased risk of myocardial infarction compared with individuals who instead received CART regimens that contained non-nucleoside reverse transcriptase inhibitors (20). In this study, a 10% increased relative risk per year of the use of protease inhibitors remained even after adjusting for other independent risk factors, including increased age, smoking, diabetes, dyslipidemia and male sex (20). Similar relationships between increasing duration of protease inhibitor-containing CART regimens and increased rates of cardiovascular disease and cardiovascular and cerebrovascular events have been found in most other studies.

The metabolic syndrome (i.e., dyslipidemia, abdominal adiposity, elevated blood pressure, and insulin resistance) is common in HIV-infected patients, and it increases with age and protease inhibitor exposure (9, 21). Compared with HIV-seronegative men, and after adjusting for age and body mass index, the incident rate of diabetes is up to four times higher among HIV-infected men using CART. Notably, the risk of diabetes is greatest with the use of stavudine, zidovudine, and didanosine, agents that cause mitochondrial depletion (22). The association between the depletion of skeletal muscle mitochondrial content, with aging, and the development of diabetes (23) suggests that the mitochondrial toxicity of nucleoside reverse transcriptase inhibitors contributes to much of the diabetes associated with CART. However, it must also be recognized that insulin resistance also occurs with the use of protease inhibitors.

In view of the similar epidemiology of HIV, hepatitis B virus (HBV) and hepatitis C virus (HCV), and the relationship between nucleoside reverse transcriptase inhibitor-induced mitochondrial toxicity and hepatic steatosis, liver disease has been a long-standing concern among HIV-infected patients. Rates of these viral hepatitises vary substantially among HIV-infected populations, being much more common in patients who acquire HIV infection by injection drug use. Predictors of liver-related deaths in HIV-infected individuals include increased age as well as CD4<sup>+</sup>cell count depletion, uncontrolled viremia, intravenous drug, HCV infection, and active HBV infection (16).

HIV-associated nephropathy (HIVAN) is a collapsing form of focal glomerulosclerosis with tubulointerstitial injury. HIVAN, which often presents as the nephrotic syndrome, is far more common among HIV-infected patients who are

African American than among those of other ancestry. Other risk factors are decreased CD4<sup>+</sup> cell counts and a family history of renal disease. Intrarenal HIV infection implicates viral replication in the pathogenesis of HIVAN. In the absence of effective treatment, HIVAN relentlessly progresses to end-stage renal disease, which may be ameliorated or prevented by the administration CART (9). Elevated rates of diabetes, hyperlipidemia, and hypertension in HIV-infected patients are likely to contribute to increased rates of advanced renal insufficiency in HIV-infected older patients.

Rates of pulmonary disease, bone disease, and cancer also are increased in HIV-infected patients. In addition to indirectly causing respiratory disease as a consequence of pneumonia, HIV infection alone is also associated with increased rates of chronic obstructive pulmonary disease and pulmonary hypertension. These associations remain significant in analyses that adjust for age, race/ethnicity, pack-years of smoking, injection drug use, and alcohol abuse (15, 24). Furthermore, compared with HIV-infected patients who receive CART regimens that do not include protease inhibitors, patients receiving protease inhibitor-containing regimens are at increased risk of having reduced bone mineral density and osteoporosis (25). Finally, an analysis that compared the relative rate of cancer in transplant and HIV-infected patients vs. the background rates in the general population found that for 20 of the 28 types of cancer there was a significantly increased incidence in both populations, suggesting that immune deficiency, rather than other risk factors for cancer, is responsible for the increased risk of cancer in both groups (26).

The concept of frailty, defined as the presence of at least three findings among unintentional weight loss, exhaustion, low physical activity level, weakness, and slowness, has been used to provide insight into the overall status of HIV-infected patients (27). By this definition, compared with HIV-negative men, HIV-infected men are 4.5–10 times more likely to be frail. The likelihood of being frail increased with age, the duration of HIV infection, having fewer than 350 CD4<sup>+</sup> cells/ $\mu$ L, or having uncontrolled viremia (>50,000 HIV-1 copies/mL of plasma). Adjusted analyses of the prevalence of frailty demonstrated that the effect of 0.1–4 years of HIV infection was greater than that of 10 years of natural aging and that HIV infection and natural aging had synergistic effects on frailty. This relationship with frailty was not explained by prior AIDS events, cigarette smoking, or recreational drug use.

## Diagnostic Tests

The benefits of identifying and treating asymptomatic HIV-infected individuals are firmly established, and testing for HIV infection is highly cost-effective (9, 28). Nevertheless, 25% of the 1.2 million HIV-infected persons in the United States remain untested and undiagnosed. Consequently, despite frequent opportunities for earlier HIV testing during patient visits to outpatient clinics, urgent care clinics, emergency rooms, and hospitals, 12–43% of newly-diagnosed patients already have

advanced immunodeficiency and/or a concurrent acute opportunistic infection (28, 29). Delayed diagnosis is even more problematic in the elderly as indicated by sero-epidemiological studies (30) and the increased rates of progression to AIDS (4) and death (1) in older vs. younger persons after the diagnosis of HIV infection.

Among the reasons for delayed diagnosis in the general population is that HIV-infected patients are largely asymptomatic prior to the onset of advanced immunodeficiency. Moreover, many persons, and especially the elderly, are unaware of their risk factors for HIV infection (e.g., prior activities of their sexual partners) or are unwilling to divulge these risk factors (e.g., injection drug use) to their medical providers. The diagnosis of HIV infection in older patients is further complicated by the fact that HIV encephalopathy and wasting syndrome, conditions that mimic many other illnesses in the elderly, are disproportionately frequent AIDS-defining diagnoses in older patients (1, 6). Finally, older minority patients comprise the population at greatest risk (4) while reporting fewer symptoms than do other ethnic/racial groups (31).

The Centers for Disease Control and Prevention (CDC) has recommended that every American aged 13–64, regardless of the presence of known risk factors, be offered HIV testing as a matter of routine clinical practice unless the prevalence of undiagnosed HIV infection in the target population is less than 0.1% (32). However, the basis for not routinely offering older patients HIV testing is not firmly established. Indeed, a blinded serosurvey done among persons undergoing blood tests at six Department of Veterans Affairs medical centers in 2000–2002 demonstrated seroprevalences of 0.7%, 0.5% and 0.1% among persons aged 55–64, 65–74 and  $\geq 75$  years of age (30). Regardless of whether routine HIV testing is implemented, persons 65 or older should be encouraged to be tested for HIV infection if they have relevant risk factors. These risk factors include a history of unprotected contact with sexual partners, whose HIV status is not known, prior injection drug use, blood transfusions in the developed world between 1978 and 1985, or surgery or blood transfusion in a developing country at any time.

For persons with established disease (i.e., chronic HIV infection), standard laboratory testing to establish a diagnosis of HIV infection consists of a screening enzyme immunoassay (EIA). If the EIA is positive, then confirmatory testing is done by means of a Western Blot or an immunofluorescent antibody assay (33). For acutely infected patients (i.e., those undergoing seroconversion reactions), it is important to recognize that HIV infection is undetectable for 7–10 days following exposure. Thereafter molecular assays (e.g., viral load tests) are able to detect HIV-1 RNA in plasma. Commercially available HIV screening tests that measure the HIV p24 antigen become positive about 2–3 weeks after infection, and, depending on the version of the test being used, HIV antibodies in the bloodstream become detectable by the enzyme immunoassay or EIA after 3–6 weeks of infection (33). Although HIV-1 RNA measurement is the most sensitive assay during seroconversion, care must be taken in the interpretation of these results, as low titer HIV-1 RNA measurements ( $< 5,000$  RNA copies/mL) in the absence of other serological indications of HIV infections are likely to represent false-positive results. In contrast, values greater than 100,000 HIV-1 RNA copies/mL are characteristic of persons with true acute seroconversion reactions (33). All patients who are

diagnosed with HIV infection on the basis of viral load results should subsequently undergo standard serological testing to confirm that the diagnosis is correct.

In addition to the standard HIV testing methods, there are now six Food and Drug Administration-approved rapid HIV tests. All use an enzyme immunoassay similar to the conventional HIV EIA tests but differ in that they are interpreted visually without further instrumentation. The 95% confidence limits of the sensitivities of these tests range from 98.5 to 100%, with specificities of 98.6-100% depending on the test and type of sample used such as oral fluid vs. whole blood (33). All reactive tests should be considered “preliminary positives” and require confirmation with a traditional Western Blot or an immunofluorescent assay (33). Performing a traditional EIA after a rapid HIV test is not recommended, as the EIA may be falsely negative. As with EIA testing, in patients with high-risk exposures and a negative rapid test, repeat testing is recommended 3 months after the initial or potential exposure. The advantages of rapid tests are that results are available within 1 h. Thus, patients can wait for the results rather than needing to return to the testing sites. Many of the rapid tests are waived from the requirements imposed by the Clinical Laboratory Improvement Amendments (CLIA), which facilitates making testing available in both medical and non-medical community settings.

Once the diagnosis of HIV infection is confirmed, subsequent laboratory testing is necessary to determine the degree of immunodeficiency, the amount of viral replication, the presence of pre-existent antiretroviral resistance, prior exposure to other infectious agents, the presence or absence of other medical comorbidities, and factors that predict the tolerability of regimens used in anti-viral therapy or in the treatment or prophylaxis of opportunistic infection (9).

Quantitation of the CD4<sup>+</sup> cell count and measurement of the viral load should be performed in all patients with newly diagnosed HIV infection. The CD4<sup>+</sup> count guides decisions to initiate CART and whether to provide prophylaxis to protect against the development of opportunistic infections. In contrast, the viral load yields prognostic information regarding the likely future rate of CD4<sup>+</sup> cell loss (9). In addition, if the viral load is >1,000 HIV-1 RNA copies/mL in confirmed HIV infection (EIA or Western blot test), genotypic testing to assess for the presence of antiretroviral resistance is recommended regardless of whether or not CART will be started as resistance to one or more classes of antiretrovirals is present in 6–16% in treatment naïve patients (9).

Standard recommended medical tests include performance of a urinalysis and chest X-ray as well as measurements of the complete blood count, electrolytes, creatinine, glucose, and transaminases. Recommended evaluations for exposures to prior infectious agents include a tuberculin skin test, culture or nucleic acid amplification tests (NAT) to detect infection by *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, and serological testing for infection by syphilis, *Toxoplasma gondii*, cytomegalovirus (CMV) and hepatitis A, B, and C. Finally, in women, a complete pelvic examination and cervical cytological examination should be performed (9, 21). Recommended age-related screening that is specific to HIV-infected patients (those over 40 years old) includes performance of an electrocardiogram (21).

Laboratory testing is also necessary to determine the safety of therapy. Thus, testing for glucose-6-phosphate dehydrogenase (G6PD) deficiency, especially in African-American patients, where deficiency is found in 10% of men and 1–2% of women, is recommended, as hemolysis can occur when patients are placed on dapsone or sulfonamides. Testing for the presence of human leukocyte antigen (HLA)-B\*5701 is now recommended prior to the use of abacavir, as the presence of this marker is highly sensitive and specific for the development of potentially life-threatening hypersensitivity reactions to this agent. Patients with a positive HLA-B\*5701 should not be given abacavir and should have abacavir listed as an allergy in the medical record (9).

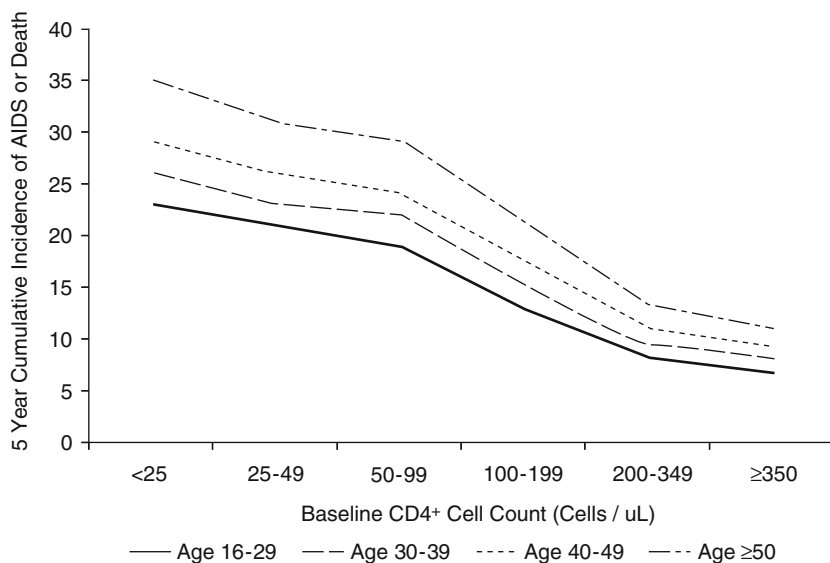
When CART is initiated, baseline measurements should be obtained to determine the viral load, CD4<sup>+</sup> cell count, complete blood count, serum electrolytes, creatinine, glucose, fasting lipid panel, and transaminases (21). The CD4<sup>+</sup> cell count, viral load, complete blood count, chemistry, and transaminases should be repeated after 4–6 weeks (21). Treated, stable persons who achieve virological suppression (i.e., a viral load <50–400 HIV-1 RNA copies/mL) and asymptomatic, untreated patients, who have CD4<sup>+</sup> counts ≥200–350 cells/μL, should have their viral load and CD4<sup>+</sup> count monitored every 3–4 months. Other laboratory tests should be obtained to monitor for adverse drug effects every 6–12 months or more frequently as clinically indicated. Finally, patients should be regularly monitored for the acquisition of new sexually transmitted diseases, latent tuberculosis infection, and viral hepatitis. The frequency of such monitoring is dependent on patient behavior and epidemiological exposure but is generally no less often than every 12 months. Readers are referred elsewhere for specific guidelines for the management of unstable patients and as regards to cardiovascular, metabolic, hepatic, renal, and other comorbidities that may arise prior to or following the initiation of antiretroviral therapy (9, 21).

## ***Treatment***

Prior to the availability of CART in 1996 there were few options for the treatment of HIV infection other than monotherapy with nucleoside reverse transcriptase inhibitors and prevention of opportunistic infections with prophylactic medications. During that era, the course of illness in HIV-infected patients was relentlessly progressive. In contrast, with the receipt of CART, even patients in the most advanced stages of disease can derive dramatic, long-lasting immunological and clinical benefit from appropriate therapy (9). These dramatic clinical benefits are mediated by treatment-induced reduction of HIV viral replication as assessed by measurements of the viral load (HIV-1 RNA copies/mL). Successful suppression of HIV replication is in turn determined by the intrinsic potency of the prescribed regimen, adherence to treatment, and the absence of resistance to the chosen antiretroviral agents (9).

CART provides substantial benefit for both older and younger HIV-infected patients (34). Indeed, older subjects are more likely to achieve virological control of HIV replication (7) and less likely to develop subsequent virological breakthrough (35). These findings are likely due to improved adherence to therapy among the elderly (7). Nonetheless, after starting CART, the subsequent risk of AIDS and/or death remains greater in older than it does in younger patients, as evident in analyses that correct for the effects of the baseline CD4<sup>+</sup> cell count, viral load, clinical stage of disease, and history of injection drug use (Fig. 4) (36).

As discussed previously, the increased prevalence of other comorbidities likely contributes to the increased rates of mortality in older HIV-infected patients. However, less complete reconstitution of immune function may also play a role, as most analyses indicate that older patients have a slower and less substantial recovery of CD4<sup>+</sup> cell counts after the initiation of CART. For example, a study of 80 subjects, with virological suppression, found that when compared with the younger patients, older HIV-infected subjects had smaller CD4<sup>+</sup> cell count increases for up to 18 months after the initiation of CART, and that with every 10 years of age the CD4 count increased by 35 cells/ $\mu$ L/year less during the first year of treatment (37). Several larger prospectively followed cohorts have also demonstrated that, despite having excellent virological responses, the rate and magnitude of the CD4<sup>+</sup> response



**Fig. 4** Cumulative incidence of AIDS or death 5 years after initiation of CART in previously antiretroviral therapy naïve patients according to CD4<sup>+</sup> cell count and age in years in persons with no history of injection drug use, no prior clinical AIDS defining diagnoses and a baseline viral load of ( $\geq$ 100,000 HIV-1 RNA copies/mL, of death in non-injection drug users vs. the most recent CD4 count



is less in older patients than it is in younger patients (7). Similarly, older patients have slower CD4+ cell recovery following receipt of cytotoxic chemotherapy (38). The findings are consistent with age-related decreases of thymic naïve CD4+ cell production (38) and with the observation that the naïve CD4+ cell count at the time of initiation of HAART correlates with the magnitude of the subsequent increase in the CD4+ count.

The November 2008 U.S. guidelines for treatment of HIV-infected adults recommend the initiation of CART for persons with symptoms referable to HIV infection, with a prior AIDS defining illness, with a CD4+ count less than 350 cells/ $\mu$ L, those who are pregnant, those who have HIV-associated nephropathy, or those who are about to receive treatment for co-infection with hepatitis B (9). The recommended initial antiretroviral therapy is a combination of two nucleoside reverse transcriptase inhibitors and either a non-nucleoside reverse transcriptase inhibitor or a protease inhibitor with adjunctive low-dose ritonavir. The specific recommended nucleoside reverse transcriptase inhibitors are a combination of tenofovir plus emtricitabine (given as the fixed combination pill Truvada®) while the recommended non-nucleoside reverse transcriptase inhibitor is efavirenz. Recommended protease inhibitors are combination of low-dose ritonavir with either lopinavir (given as the fixed combination medication Kaletra®) or with darunavir, fosamprenavir, or atazanavir. Guidelines also provide recommendations for alternative regimens for patients who cannot tolerate these drugs and for the treatment of patients with virus resistant to these agents (9). A full discussion of these aspects of treatment or of the agents within all six classes of approved antiretroviral agents, including the two newest classes (i.e., the CCR5 co-receptor inhibitor maraviroc or the integrase inhibitor raltegravir) is beyond the scope of this chapter; however, it is important, for practitioners using any of these drugs to be aware of the many drug–drug interactions, especially with the non-nucleoside reverse transcriptase inhibitors and protease inhibitors, which each have multiple effects on cytochrome P450 isoenzymes, as well as with the adverse effects of these drugs. The importance of these issues to the elderly is self-evident.

Whether the current treatment guidelines, which recommend initiation of CART in most patients only after the CD4+ cell count falls to <350 cells/ $\mu$ L, are fully applicable to older patients has not been assessed by prospective clinical studies. The more rapid progression of HIV disease, age-related immune senescence which may be independent of the CD4+ count, the increased prevalence of comorbidities which may be exacerbated by HIV infection, and decreased rates of immune reconstitution provide a plausible rationale for beginning therapy at higher CD4+ cell counts in older patients. However, models of patient survival following the initiation of CART indicate that competing morbidities and greater susceptibility to adverse drug effects may, in this population, diminish the benefits of earlier antiretroviral therapy (39). In particular, modeling indicates that while persons 30 year of age consistently derive increased life expectancy and quality adjusted life years by starting antiretroviral therapy at a CD4+ count of 500 rather than 350 cells/ $\mu$ L regardless of the viral load, 40 year old individuals do not benefit from earlier CART unless the viral load is  $\geq$ 30,000 HIV-1 RNA copies/mL, and 50 year olds do

not benefit from earlier therapy unless the viral load is  $\geq 300,000$  HIV-1 RNA copies/mL (39).

In addition to providing antiretroviral therapy, it is important to be aware of the indications for the use of prophylactic medications to prevent opportunistic infections in HIV-infected individuals. All HIV-infected persons with a positive tuberculin skin test (defined as  $\geq 5$  mm of induration) should, after active tuberculosis is excluded, receive therapy for latent tuberculosis infection (see also chapter “Tuberculosis in Older Adults”). For persons with  $< 200$  CD4<sup>+</sup> cells/ $\mu$ L or in whom the percentage of CD4<sup>+</sup> cells is  $< 14\%$  (40), prophylaxis should be administered to prevent PCP, preferably with a fixed-dose combination of daily trimethoprim/sulfamethoxazole. For persons with CD4<sup>+</sup> cell counts  $< 100$  cells/ $\mu$ L who also have serological evidence of prior exposure to toxoplasmosis, prophylaxis should be given to prevent reactivation of this pathogen (again with a fixed-dose combination of daily trimethoprim/sulfamethoxazole or a combination of dapsone plus pyrimethamine). In addition, for persons with  $< 50$  CD4<sup>+</sup> cells/ $\mu$ L, weekly azithromycin should be used as prophylaxis against disseminated infection by *Mycobacterium avium* complex (40). Persons with  $< 50$  CD4<sup>+</sup> cells/ $\mu$ L who have serological evidence of prior CMV infection should also have fundoscopic examination to exclude clinically silent retinitis due to this pathogen. Finally, HIV-infected patients should be offered influenza vaccination, pneumococcal vaccination and, if non-immune, vaccinating against hepatitis A and hepatitis B. For further details and unusual circumstances, readers should refer to more detailed references (9, 40).

## Prevention

Discussions about HIV infection are especially important among older individuals who have become newly single due to divorce or loss of their mates. Many older patients lack awareness of the risk factors for getting HIV, due to the lack of HIV prevention education targeted at older people, or to having ignored HIV prevention messages. Consequently, older individuals often have no training in safer sexual activities and are less likely to use barrier precautions to prevent procreation. Furthermore, use of medications for erectile dysfunction in men increases the likelihood of risky activities while the development of atrophic vaginitis in women increases the likelihood of infection, if the partner is infected. Measures to prevent HIV infection include use of male or female condoms (latex or polyurethane) during sexual intercourse, ensuring that sexual partners have been tested and are HIV-uninfected, and not sharing needles or any other equipment used to inject drugs.

As previously discussed, Americans past the age of 50 years, with a known behavioral risk for HIV infection, are much less likely to have undergone HIV testing. Because of the differences in the sources of information used and trusted by older persons, there is a need to develop new educational and intervention strategies targeted to this age group. Of note, older individuals prefer to receive prevention education through presentations at centers, which serve older adults, such as churches

and retirement communities, as well as from physicians and other healthcare providers. As patients older than 50 years are unlikely to ask questions concerning HIV or AIDS, physicians need to proactively address these issues. This will require a change in habit as most physicians are less likely to discuss HIV or AIDS with patients older than 50 years than with younger persons (3).

Prevention care is also important for older persons who are already known to be HIV-infected. Important prevention education includes discussions of the use of barrier precautions during sexual encounters to protect against transmission of HIV to uninfected partners and to protect the index patient from the acquisition of new sexually transmitted diseases or re-infection by a potentially more resistant HIV isolate. Frank discussion of these issues is likely to be particularly important in persons receiving therapy for erectile dysfunction. Similarly, healthcare providers should refer HIV-infected patients with alcohol or substance dependency to appropriate treatment programs and provide information regarding risk-reduction strategies to patients who do not enter such programs. Providers will need to be increasingly familiar with such referrals and counseling, as the proportion of older HIV-infected patients, who have a history of injection drug use, increases.

## Conclusion

Perhaps the most important aspect of HIV in the elderly is the under-recognition of the incidence and prevalence of this infection in the older population. While the increasing prevalence is due largely to the increased survival of younger HIV-infected individuals, an increasing proportion of new diagnoses of HIV infection are occurring in older individuals. Unfortunately, healthcare workers offer HIV testing to asymptomatic older individuals less often; they also consider HIV/AIDS less frequently in acutely ill older patients, even among persons who are subsequently found to have PCP. Furthermore, clinical manifestations of HIV infection in the elderly contributes to diagnostic confusion, as older HIV-infected patients less often complain of HIV-related symptoms and more often have findings suggesting age related neurocognitive decline.

Regardless of the underlying explanation, failure to consider HIV in the elderly contributes to the increased likelihood of older HIV-infected persons to present with advanced immune suppression and to die during hospitalizations for PCP or within the year of the diagnosis of HIV infection. Nevertheless, once identified with HIV infection, older patients have excellent adherence to therapy, excellent virological responses and, although immunological responses are somewhat less robust, substantial benefit from antiretroviral therapy (34). However, due to pre-existing conditions or adverse effects from antiretroviral therapy, the management of older patients is complicated by increased prevalence of comorbidities (7, 9).

In closing, providers should follow the recommendation of the CDC that all persons between the ages of 13 and 64 should be routinely offered HIV testing, regardless of the presence of any known risk factor for infection (32). Strong arguments

can also be made for routine testing of persons over the age of 64 (30). Providers who choose not to routinely offer HIV testing for those over the age of 64 should take care to identify HIV risk factors in older patients and to offer testing to individual who have such risk factors. Finally, HIV prevention education has relevancy for older as well as for younger patient populations.

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# SARS and West Nile Virus

**Mark B. Loeb**

## **Key Points**

- Clinical presentation of SARS is nonspecific; the important clinical findings in West Nile virus infection are those associated with neurological complications.
- Rapid and accurate diagnosis of SARS and West Nile virus infection remains an important clinical challenge.
- Older adults are at higher risk of complications, including death from SARS and West Nile virus.
- At present, there is no effective therapy for these infections.
- Although efforts are under way, there are presently no effective vaccines for SARS or West Nile virus.

## **Introduction**

In 1992, the Institute of Medicine defined emerging infections as “new, reemerging or drug-resistant infections whose incidence in humans has increased within the past two decades or whose incidence threatens to increase in the near future” (1). Recently it has become evident that severe acute respiratory syndrome (SARS) and West Nile virus are emerging infections that can pose an important threat to the health of older adults. This chapter will focus on SARS and West Nile virus and will summarize available evidence of the impact of these infections on older adults.

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## Severe Acute Respiratory Syndrome

### *Epidemiology and Clinical Relevance*

SARS has been documented in over 8,400 persons globally, with cases in Asia, Europe, and North America. A novel coronavirus has been identified as the etiologic agent. In November 2002, the first cases of SARS arose from Guangdong province, in the south of China. On February 13, 2003, based on initial reports from the Chinese government, the outbreak was officially recognized by the World Health Organization. Unfortunately, over the next 5 months, many more deaths ensued.

Both the global and local spread of SARS is related to so-called “super-spreading” events. In late February 2003, a critical event for the global spread of SARS occurred at the Hotel Metropol in Hong Kong. A physician who had treated hospitalized patients in the city of Guangzhou, and who was symptomatic with SARS during his stay in Hong Kong, became the source of infection for 12 people, the majority of whom were staying on the same floor as him. These individuals, also tourists, eventually sought medical care in hospitals in Hong Kong, Vietnam, Singapore, Ireland, the United States, and Canada. There was secondary spread in all these countries with the exception of United States and Ireland.

Spread of SARS occurred primarily within the healthcare setting. The secondary spread that occurred, predominantly in acute care hospitals, was largely attributed to a failure to recognize a new respiratory syndrome along with the associated delay in assuming appropriate infection control precautions soon enough. Fortunately, the spread of SARS to elderly residents of long-term care facilities was limited. However, transfer of patients to a nursing home did lead to a secondary spread in Hong Kong (2). The incubation period of SARS, estimated to range from 2 to 10 days, with a mean incubation period of 6 days, is sufficiently long enough for some people to be pre-symptomatic on admission and later develop symptoms. Importantly, there is no evidence that individuals who are asymptomatic can transmit the virus. The incidence of asymptomatic infection appears to be very low. In fact, in the Toronto outbreak fewer than 2% of healthcare workers, who had multiple exposures to SARS patients, developed serological evidence of infection.

The reproductive number of the SARS coronavirus, that is the expected number of infectious secondary cases generated by an average infectious case in a completely susceptible population, has been estimated to range from 2.2 to 3.7 (3). This figure is not particularly high as compared with the reproductive numbers of other respiratory viruses spread by respiratory droplet aerosol such as influenza or measles. The clinical experience with SARS reflects this (i.e., once appropriate infection control precautions are instituted, the virus can promptly be contained and transmission stopped). The fact that SARS, unlike influenza for example, is not efficiently transmitted in the community supports this as well. The notable exceptions to the lack of community transmission was the spread at the Hotel Metropol, where it is hypothesized that the virus detected by polymerase chain reaction (PCR) in vomit near the index case’s room or elevator may have been the source of environmental transmission.



Community spread also occurred at Amoy garden, an apartment complex, in Hong Kong; the leading hypothesis in this case was that that sewage contaminated with small virus-containing droplets entered the bathrooms of the apartment complex through dried-up U traps (4). A comprehensive review of all the cases of SARS in Hong Kong showed that the transmissibility of viral infection was low, with the exception of settings where intimate contact or where clinically significant contamination occurred (5).

The epidemiologic evidence suggests that within hospitals the transmission mode of SARS was by droplet, although limited aerosol transmission may have also played a role. Super-spreading events, defined as spread from one source patient to many others, played an important role in transmission of the disease. In one report of SARS transmission in a Beijing hospital, patients linked to super-spreading tended to be older, more ill, had more contacts, and were more efficient at spreading the virus as compared with other source patients who were not linked to super-spreading (6).

To date, there have been a number of studies that have addressed risk factors for acquiring SARS. There is no evidence to suggest that the elderly are prone to infection with SARS; however, there is ample evidence that outcomes are worse. A consistent finding is that exposure to aerosol generating procedures is high risk. For example, a retrospective cohort study in a Toronto hospital revealed that assisting with intubation as well as suctioning prior to intubation was associated with a fourfold risk of acquiring SARS among critical care nurses (7). Manipulation of an oxygen mask resulted in a ninefold increased risk to nursing staff. Studies to further define risk factors among household contacts and hospitalized patients are ongoing.

SARS is caused by a novel strain of coronavirus (SARS-CoV) believed to have originated from an animal in southern China such as a masked palm civet. Coronaviruses are single-stranded RNA viruses known to cause illness in both animals and humans. The virus belongs to a new group within the coronavirus family. An important feature of the SARS-CoV is that, unlike other respiratory viruses, the viral load increases until about the tenth day of illness, and then it diminishes (4). This has implications for infection control precautions and also clinically ones. If a case is put into isolation before the viral load has peaked, then the chance of secondary transmission can be lessened. Clinically, after the first week of illness, one often sees a worsening of symptoms. Molecular epidemiologic studies reveal that the SARS-CoV from outbreaks in Hong Kong, Vietnam, Singapore, Toronto, and Taiwan are clonally related whereas those from Guangdong province are more diverse genetically (4). This may imply that some molecular lineages are more likely to be transmitted than others.

### *Clinical Manifestations*

At presentation SARS is characterized by fever, myalgia, cough, chills, or rigors. Unfortunately, this syndrome is nonspecific, and the clinical features cannot be used to distinguish it from other viral or bacterial respiratory syndromes.

**Table 1** Risk factors for poor prognosis in severe acute respiratory syndrome (SARS)

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Older age
Co-morbidity
High viral load

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The most common symptom is fever, occurring in virtually all cases; shortness of breath occurs later in the illness. Some patients have diarrhea; others have nausea and vomiting. In the elderly, SARS may present as an afebrile illness, where malaise and decreased appetite are the main features. Alternatively, it can present with a low-grade fever with few respiratory symptoms (8). When compared with younger patients who have SARS, older patients are less likely to present with fever, chills, and diarrhea (9). This pattern is similar to community-acquired pneumonia, where symptoms and signs of pneumonia are less distinct in older adults.

There are a number of factors associated with a poor prognosis in SARS (see Table 1). An important factor is older age; studies have shown that older patients are at substantially higher risk of death. In a study from China, the mortality rate among patients aged 50 years and over was 13 times that for patients aged <50 years (10). In another study, every 10-year increase in age was associated with twofold increase in death (11). In a study from Hong Kong, multivariate analysis revealed that those who are older than 60 years (relative risk, 5.10; confidence interval (CI), 2.30–11.31];  $P < 0.001$ ) and lactate dehydrogenase level greater than 3.8  $\mu\text{kat/L}$  at presentation (relative risk, 2.20 [CI, 1.03–4.71];  $P = 0.04$ ) were independent predictors of mortality (12). Comorbidities, especially diabetes mellitus but heart disease as well, have also been repeatedly demonstrated to be risk factors for adverse outcomes in SARS (4). The aforementioned risk factors were noted in a Toronto study of 196 patients with SARS (13). Thirty-eight (19%) SARS patients became critically ill. The interquartile range age of the 38 patients was 57.4 (39.0–69.6) years. The median duration between initial symptoms and admission to the intensive care unit was 8 (5–10) days. Twenty-nine (76%) required mechanical ventilation. At 28 days, mortality was 13 (34%) of 38 patients, and for those requiring mechanical ventilation, mortality was 13 (45%) of 29. At 28 days, six patients (16%) remained mechanically ventilated. By 8 weeks' follow-up, two of these patients had died. Patients who died were more often older, had preexisting diabetes mellitus, and on admission to the hospital were more likely to have bilateral radiographic infiltrates (13). High viral load at presentation can also be associated with poor outcomes. In a prospective study from Hong Kong, the following factors were independently associated with worse survival: older age (61–80 years) (adjusted hazard ratio (HR), 5.24, 95% CI 2.03–13.53), presence of an active comorbid condition (adjusted HR 3.36, 95% CI 1.44–7.82) and higher initial viral load of SARS coronavirus, according to quantitative PCR of nasopharyngeal specimens (adjusted HR 1.21 per  $\log_{10}$  increase in number of RNA copies per milliliter, 95% CI 1.06–1.39) (14).

Along with increased lactate dehydrogenase, elevated serum creatinine kinase and alanine aminotransferase are often seen in SARS. These laboratory indices, however, cannot discriminate SARS from other respiratory infections. In the majority

of patients with SARS, the chest radiograph is abnormal; the most common abnormalities being ground-glass opacifications. Again, however, these findings are not specific for SARS.

### ***Diagnostic Tests***

Making the diagnosis has been one of the most important challenges of SARS. The lack of an accurate real-time diagnostic test allowed SARS to be spread in hospitals around the world. SARS can be diagnosed very accurately retrospectively using serology. That is, antibodies to the virus will appear in over 95% of infected patients at least 21 days (but preferably 28 days) or longer after onset of symptoms. Although this is of important epidemiologic value, it is not helpful to the front-line clinician who must decide if a patient has SARS. A number of groups are working on developing nucleic acid amplification tests such as reverse transcription-PCR; however, none of these tests has proven to have a sufficiently high positive or negative predictive value to date. For example, in one recent report the highest detection rate was 75% between days 5 and 7 of illness (15). Although SARS-CoV is readily cultured, the infection control risks to laboratory workers do not make routine culturing of the virus an attractive option. Other types of assays being studied, including immunoblot assays and radioimmunoassays, are still in a development phase. The utility of individual clinical symptoms in diagnosing SARS is limited. However, clinical prediction rules, where constellation of symptoms and signs are used to diagnose, can be of benefit to clinicians in the setting of a SARS outbreak. For example, in a study from Hong Kong, the sensitivity of a clinical prediction rule was 90%; however, specificity was lower at 62% (16).

### ***Treatment***

There are a number of agents that have been proposed as therapy for SARS. However, there have not been any randomized controlled trials of therapy to document efficacy. Ribavirin, a synthetic nucleoside antiviral agent with inhibitory activity against both DNA and RNA viruses, was commonly used during the SARS outbreak. Usually in an aerosolized form, it has been used, in both adults and children, for the treatment of respiratory syncytial virus pneumonitis. The combination of oral ribavirin and interferon has also been shown to be efficacious in the treatment of chronic hepatitis C. High-dose intravenous ribavirin has been used in the treatment of Lassa fever and hemorrhagic fever with renal syndrome. The theoretical rationale for using this agent was that it was known to have *in vitro* activity against other respiratory viruses, including respiratory syncytial virus and influenza; also its use began before the agent of SARS was fully defined. There are no systematic evaluations of efficacy of ribavirin for SARS. However, there are reports of toxicity.

In Toronto, 61% of patients with SARS who were treated with ribavirin developed hemolytic anemia. Hypocalcemia and hypomagnesemia were reported in 58 and 46% of patients, respectively (17).

There have been reports of benefit with treatment from high-dose corticosteroids; however, there have been no randomized controlled trials to substantiate efficacy (18). One concern about these regimens is long-lasting adverse reactions such as avascular necrosis and neuromuscular sequelae. One study has confirmed that in patients with SARS, who were treated with corticosteroids, cumulative dose of prednisone is an important risk factor for developing osteonecrosis of the hip and knee.

There is theoretical and limited clinical data suggesting a role for interferon-alpha in the treatment of SARS. Evidence exists that prophylactic treatment of SARS coronavirus-infected macaques with the pegylated interferon-alpha significantly reduces viral replication and excretion, viral antigen expression by type 1 pneumocytes, and pulmonary damage compared with untreated macaques. In a study of 22 patients with probable SARS, interferon treatment was associated with a shorter time to resolution of radiologic infiltrates, better oxygen saturation, less of an increase in creatine kinase, and more rapid resolution of lactate dehydrogenase.

## ***Prevention***

There are many groups that are presently working on a vaccine against the SARS coronavirus. One of the obstacles they have faced has been the inability to find an animal model where the disease manifestations are reliably reproduced when the animal is challenged with the virus. Once an animal model can be found, then testing where these animals are vaccinated then challenged with the SARS Co-V can begin. Research groups are currently working on vaccines using inactivated virus, recombinant virus, and plasmid DNA vaccines.

In the absence of a vaccine, surveillance measures are an important strategy for preventing the spread of SARS. Use of personal protective equipment is also important. Evidence exists suggesting that use of a mask can reduce the relative risk of SARS by 80% in critical care units (7).

## **West Nile Virus**

### ***Epidemiology and Clinical Relevance***

In North America, West Nile virus (WNV) has emerged as an important human pathogen. In 1937, the virus, a type of flavivirus, was first isolated from the blood of a febrile patient in northern Uganda. Outbreaks of West Nile fever and meningoencephalitis have since been described in many parts of the world, including

Africa, Europe, the Middle East, and Asia (19). The first North American outbreak was in 1999 in New York City (20), where 62 cases of WNV meningoencephalitis were reported. In late August 1999, a physician in Queens, New York, recognized an unusual cluster of elderly patients with viral encephalitis. These cases were initially thought to be St. Louis encephalitis; however, follow-up serologic and virologic investigation revealed that the cases were caused by WNV. Subsequent epidemiologic studies, however, suggested widespread transmission in New York City, with thousands of infections in the city. Sequence data from the infecting virus suggested that it was imported from the Middle East. Since then, there have been annual outbreaks of WNV across the United States and Canada.

West Nile virus is transmitted to humans through the bite of infected mosquitoes, primarily the *Culex* species. West Nile virus is maintained in nature in a transmission cycle that involves primarily birds and mosquitoes. Mosquitoes become infected when they feed on infected birds, where the virus is amplified (e.g., in robins and sparrows, in which a high degree of viremia is seen). Humans and other mammals are “dead-end” or incidental hosts. In late August and early September, the peak incidence of human disease in North America occurs. Predicting the temporal characteristics of future WNV transmission seasons, based on limited reports available to date, is not possible.

Recently, in North America, there has been a dramatic increase in the incidence of human cases of WNV (21). In 2007, there were 3,576 human cases of WNV infection reported to the Centers for Disease Control Prevention, and 353 cases reported in Canada, the highest number reported annually since WNV was first detected in 2002.

### ***Clinical Manifestations***

The pathological changes within the central nervous system due to WNV, an enveloped RNA virus, appear to be due to several factors, including the direct result of viral proliferation within neuronal and glial cells, cytotoxic immune response to infected cells, diffuse perivascular inflammation, and microglial nodule formation (22–23). The range of clinical manifestations of WNV infection is, however, highly variable (Table 2). Fever, headache, and fatigue are common while skin rash on the trunk, swollen lymph glands, and eye pain occasionally are seen. The incubation period is thought to range from 3 to 14 days.

**Table 2** Clinical presentations of West Nile virus infection

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West Nile fever
Meningitis
Encephalitis
Acute flaccid paralysis
West Nile poliomyelitis

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Of infected persons, approximately 20% experienced mild symptoms (“West Nile Fever”), and about 1% develop meningitis, encephalitis, or acute flaccid paralysis (24). The incidence of such severe neurological syndromes increases with age. Thus, older adults are at increased risk for developing neuroinvasive disease. Although less common, other syndromes include peripheral neuropathy, polyradiculopathy, and optic neuritis.

When the central nervous system is affected, clinical syndromes ranging from febrile headache to aseptic meningitis to encephalitis may occur, and these are usually indistinguishable from similar syndromes caused by other viruses.

About 60–75% of people with neuroinvasive WNV infection, reportedly have encephalitis or meningoencephalitis, which is characterized by altered mental status or focal neurologic findings.

West Nile encephalitis, the most severe form of neuroinvasive West Nile viral disease, manifests as fever and headache, but there are more global symptoms. Usually, there is an alteration of consciousness, which may be mild and result in lethargy but may progress to confusion or coma. Focal neurologic deficits, including limb paralysis and cranial nerve palsies, may be observed; also noted have been tremors and movement disorders.

West Nile poliomyelitis, a flaccid paralysis syndrome associated with WNV infection, is less common than meningitis or encephalitis. This syndrome is generally characterized by the acute onset of asymmetric limb weakness or paralysis in the absence of sensory loss. Pain sometimes precedes the paralysis. The paralysis can occur in the absence of fever, headache, or other common symptoms associated with WNV infection. Involvement of respiratory muscles, leading to acute respiratory failure, can sometimes occur.

Recent studies of persons infected with WNV report that symptoms and signs such as fatigue, psychological dysfunction, and motor abnormalities, can persist for months after the onset of symptoms (25, 26). Existing reports provide valuable information on self-reported outcomes but have limitations, including single follow-up assessments, follow-up at  $\leq 12$  months after symptom onset, and lack of validated instruments to measure physical and mental functioning. Moreover, factors associated with slower recovery are unknown.

## ***Diagnostic Tests***

The diagnosis of WNV is typically made by an IgM antibody capture enzyme-linked immunosorbent assay (ELISA). The diagnosis can also be made if IgM is detected in the spinal fluid. One limitation of the ELISA test is that the antigen can cross-react with other flaviviruses such as dengue. Because serum IgM antibody may persist for more than a year, it is important to determine whether the antibody is the result of a WNV infection in the previous year and unrelated to the current clinical presentation. To confirm the diagnosis of WNV infection, a plaque reduction neutralization assay can be performed, although this is typically used for research purposes.

## ***Treatment***

There is no proven therapy for WNV infection. Management is mainly supportive for those persons with neuroinvasive disease, often involving hospitalization, intravenous fluids, respiratory support, and prevention of secondary infections for patients with severe disease.

Ribavirin in high doses and interferon alpha-2b were found to have some activity against WNV in vitro, but no controlled studies have been completed on the use of these or other medications, including corticosteroids, antiseizure drugs, or osmotic agents, in the management of WNV encephalitis.

## ***Prevention***

Although clinical trials of human vaccines are in various stages of development, at present there is no available human vaccine. Use of personal protective behavior, including mosquito repellent, wearing shirts with long sleeves, long pants, and avoidance of mosquitoes can substantially reduce risk. Source reduction such as removing standing water around the home, may also reduce risk.

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