made by histologic findings on liver biopsy combined with detection of HEV RNA in blood and/or liver tissue. Currently, there are no proven effective preventive or therapeutic options for HEV infection in organ transplant recipients, although small series reported a benefit of ribavirin monotherapy.[241]

DONOR-TRANSMITTED INFECTIONS

(See Chapter 304)

An estimated 0.2% to 1% of the transplantations are complicated by donor-derived infections, and this rate is expected to increase as a result of improved recognition and reporting of these events. Although infrequent, the donor-derived infections are associated with substantial morbidity and mortality; deaths occurred in 40% of the recipients with documented transmissions.[242] Viral infections account for nearly one-third of all confirmed donor-derived infections. Transmission of certain viruses, for example, CMV, EBV, HCV, and HBV, is expected to occur predictably (Table 308.14). However, the risk can be mitigated by use of appropriate prophylactic measures in the recipient with minimal impact on posttransplantation outcomes. Unexpected donor-derived infections, for example, lymphocytic choriomeningitis virus, rabies virus, West Nile virus (WNV), and HIV have been documented with devastating sequelae. These infections have occurred when the disease was not suspected or recognized in the donor at the time of death. Other potentially transmissible agents are depicted in Table 308.14.

Donor-Derived Bacterial Infections

An estimated 5% of the organ donors may have bacteremia,[243] with the potential of transmission being greater with gram-negative bacilli, multidrug-resistant organisms, or bacteria resistant to the perioperative antibiotics used. In addition, contamination during organ procurement or donor respiratory tract colonization (in lung transplantation) may result in transmission of bacterial infections. Organs from donors with meningitis due to *Pneumococcus, Meningococcus,* and *Haemophilus influenzae,* and so forth, may be successfully transplanted, provided both the donor and the recipient are appropriately treated. Donors with documented bacterial infections should receive at least 24 to 48 hours of appropriate antibiotics before organ procurement, preferably with evidence of clinical response with continuation of antibiotics in the recipient for 7 to 14 days after transplantation.

Donor-Derived Fungal Infections

Candidiasis is the most common donor-transmitted mycoses. Most cases are due to contamination of preservation fluid and have occurred in kidney transplant recipients.[244] Donors with cryptococcosis, including those with unrecognized cryptococcal meningoencephalitis may transmit this yeast with the allograft. Active histoplasmosis or undiagnosed and presumably asymptomatic infection in the donor that had not resolved by the time of death can result in donor-derived histoplasmosis. Potential donors from an endemic area with either active or occult infection can also transmit coccidioidomycosis. Rare instances of aspergillosis and other filamentous fungi, including agents of mucormycosis have also been transmitted from infected donors. More recently, these fungi have emerged as a serious complication of transplantation tourism (the practice of traveling abroad to commercially acquire an organ) and have been associated with graft loss or death in 76% of the cases.[245]

Other Pathogens With Potential for Transmission With the Allograft

In general, donors with undiagnosed meningoencephalitis are not considered suitable for donation as transmission of not only fungal pathogens but other diseases, including prion infections, rabies, WNV, *Balamuthia,* or noninfectious entities, such as lymphomas and leukemias. Clusters of transplant-associated *Balamuthia mandrillaris* infection and another type of free-living ameba have been reported.[246] Organ transplantation from donors with primary amebic meningoencephalitis caused by the free-living ameba *Naegleria fowleri* was not associated with transmission of the infection.[247] Nevertheless, the risk of transmission of *N. fowleri* by donor organs is not fully known, and transplantation with an organ possibly harboring *N. fowleri* should be carefully weighed on an individual basis against potentially greater risk of dying from delayed transplantation. Heart transplant donors and recipients should be serotested for toxoplasmosis. Given the paucity of cysts in noncardiac tissue, screening of nonheart donors for toxoplasmosis is not routinely

TABLE 308.14 Suggested Screening for Transplant Recipients and Donors

PATHOGEN OR INFECTION	DONOR	RECIPIENT	RECOMMENDATION
Human immunodeficiency virus	+ – +	– + +	Reject Accept Ongoing studies
Human T-cell leukemia virus 1	+	±	Accept (after appropriate patient consent)
Cytomegalovirus, Epstein-Barr virus, herpes simplex virus, varicella-zoster virus	±	±	Accept
Toxoplasma gondii	±	±	Accept; D^+/R^- heart transplants at highest risk and need prophylaxis
Hepatitis C virus	Ongoing studies		
Hepatitis B virus			$HBsAg^+$ donors may be considered after careful risk and benefits assessment and appropriate patient consent; donor liver disease should be excluded histopathologically Organs from $HBsAg^-$, anti-HBc^+ donors can also be considered on an individual basis after appropriate patient consent
Syphilis (rapid protein reagent)	+	±	Accept (after appropriate patient consent) and treat recipient
"Encephalitis"	Yes		Generally reject
Tuberculosis	Purified protein derivative/interferon (IFN)-γ release assay positive (living donor)	Purified protein derivative/IFN-γ release assay positive or negative	Careful history, imaging as appropriate; treat living donors for latent tuberculosis. For recipients on the waiting list, treat for latent tuberculosis and proceed with transplantation to complete the course posttransplantation. May delay treatment for latent tuberculosis until posttransplantation in decompensated cirrhosis. Reject organs from deceased donors with active tuberculosis
Strongyloides	Screen recipients from endemic areas (stool examination and serology)		
Coccidioides	Screen recipients from endemic areas (serology)		
Histoplasmosis	No utility of routine serologic testing		
Trypanosoma cruzi	+		Generally avoid donor, although mismatches have been performed (endemic regions)

D^+/R^-, Seropositive donor/seronegative recipient; *HBsAg,* hepatitis B surface antigen.

performed. Donor screening for Chagas disease should be performed in those who have lived or traveled in an endemic area.

APPROACH TO FEVER IN THE TRANSPLANT RECIPIENT

Fever after organ transplantation should be deemed a marker of infection until proven otherwise. Although the posttransplantation immunosuppressive regimen may result in lower maximum body temperatures, it does not abolish the inflammatory response. Indeed, transplant recipients are able to mount a robust physiologic response to infection that is comparable to that seen in nontransplant patients.[248] Although antimetabolite agents, such as mycophenolate or azathioprine, appeared to suppress the febrile response, corticosteroids had little effect on the systemic inflammatory response in transplant recipients with bacterial or fungal infections.[248] Therefore most transplant recipients with an infection will have a fever, and most fevers will have an infectious etiology in this setting.[64] Febrile episodes occurring in liver transplant recipients in the ICU were due to infections in 87% of cases.[249] Noninfectious etiologies should always be considered once an evaluation for infection has been completed, including allograft rejection, vascular complications, drug fevers, and malignancy.

Fever Without an Evident Source

Some patients with fevers will not have a readily evident source on initial evaluation.[250] However, a study in transplant recipients documented that an etiology of fever of unknown origin was ultimately determined in 68% of the patients, and in 45% the cause was an infection.[251] Unlike in the general population, rheumatologic disorders were rare, and drug fever was the most common noninfectious etiology of fever of unknown origin in transplantation setting.[251]

In cases of fever of unknown origin the history of prior infections, both active and latent, should be diligently sought. Epidemiologic exposure and travel history should be obtained. Otherwise infrequently encountered opportunistic pathogens, such as cases of *Talaromyces* (previously *Penicillium marneffei),* have been documented in transplant recipients with travel to endemic areas (Southeast Asia).[252] A list of all active and recently discontinued prophylactic antimicrobials should be reviewed to determine which pathogens could potentially lead to breakthrough or postprophylaxis infections. Review of donor information is also an important consideration. Testing for unusual pathogens, such as *Bartonella, Coxiella*, and *Brucella,* should be undertaken on a case-by-case basis.

In patients with refractory fevers, cytopenias, ongoing clinical deterioration, rare entities, such as thrombotic thrombocytopenic purpura, GVHD, and hemophagocytic lymphohistiocytosis should be considered. The latter is a disorder of dysregulated immune activation, can occur after viral infections, such as CMV or EBV, carries a mortality rate of about 52% in transplant recipients, and can be difficult to diagnose.[253] Treatment is mainly supportive and involves reversal of the underlying cause, although etoposide combined with corticosteroid therapy has been attempted.

VACCINATION IN ORGAN TRANSPLANT CANDIDATES AND RECIPIENTS

The burden of vaccine-preventable infections is increased in immunosuppressed patients, including recipients of organ transplants. Routine assessment and update of vaccinations prior, rather than after, transplantation is recommended because live vaccines are generally contraindicated posttransplantation and because the immunogenicity of vaccines is typically lower in patients receiving immunosuppression posttransplantation. In addition to routine age- and immunosuppression-recommended vaccines, an assessment of the need for future travel-associated vaccines should be done because immunosuppressed patients are at higher risk for complications of travel-associated infections and because certain travel-associated vaccines are absolutely contraindicated posttransplantation (e.g., yellow fever virus vaccine). Where appropriate, laboratory measures of immunity to determine need for vaccination and response to vaccination should be assessed using established criteria (varicella, mumps, measles, rubella, hepatitis A and B). Live vaccines should be administered at least 4 weeks before transplantation. In addition, age-appropriate vaccination of family members and other close contacts is recommended. Most live vaccines can safely be administered to close contacts, but precautions to prevent transmission for certain live vaccines are recommended (rotavirus, varicella-zoster virus, live-attenuated influenza virus, oral polio virus). A summary of recommendations by the American Society for Transplant Infectious Disease Community of Practice for vaccination of adult transplant candidates/recipients is shown in Table 308.15.[254]

Selected Specific Vaccines

Influenza

Despite increased severity of influenza in organ transplant recipients, the rates of vaccination are suboptimal, and there is evidence of safety and protection against influenza-associated complications. A number of inactivated vaccine formulations are available, but no definitive clinical evidence to recommend any particular formulation. Vaccination during the influenza season should be done before transplantation when feasible. The immunogenicity of influenza vaccination is reduced after transplantation but is safe. For patients not immunized before transplantation during the influenza season, vaccination is typically deferred until 3 to 6 months posttransplantation because of diminished immunogenicity. However, in the setting of widespread influenza activity, immunization has been done as early as 1 month posttransplantation. A variety of approaches have shown improved laboratory-assessed immunogenicity, including use of higher-dose formulations and booster vaccination, but none have been designed to assess for improved clinical end points.

Pneumococcus

Current US guidelines for at-risk adults, including patients with medical conditions commonly found in transplant candidates and immunosuppressed patients, recommend a combination of a protein-conjugated vaccine that may lead to the formation of memory cells and a 23-valent polysaccharide vaccine. For adults not previously vaccinated, the protein-conjugated vaccine should be administered first, followed by the polysaccharide vaccine at least 8 weeks later.

Herpes Zoster

Immunosuppressed persons, including transplant recipients, are at significantly increased risk for zoster and associated complications. A live-attenuated vaccine (Zostavax) that reduces zoster burden by ≈50% is currently recommended in the United States for adults older than 60 years but is contraindicated posttransplantation and should be given to eligible transplant candidates at least 4 weeks before transplantation. The efficacy of this vaccine for preventing post-transplantation zoster has not been formally assessed. An adjuvanted subunit vaccine was recently FDA approved for adults older than 50 years and is theoretically not contraindicated posttransplantation, but its efficacy has not been assessed in the posttransplantation setting.[255] In a general population the subunit vaccine was shown to be immunogenic and highly effective (≈90%) and has also been studied in patients who previously received the live-attenuated vaccine. The subunit vaccine is associated with a relatively high rate of local and systemic reactions, thought to be related to the adjuvant system. Whether the adjuvant system might increase the risk for nonspecific immune activation and development of alloantibodies (anti–HLA or donor-specific antibodies) that might increase for allograft rejection is unknown. Unresolved issues include whether the subunit vaccine should be administered routinely to otherwise eligible posttransplantation patients, which of the vaccines (or both) should be administered to transplant candidates, and whether revaccination will be required.

Hepatitis B

Transmission of hepatitis B with an organ transplant is an important consideration because 2% to 9% of donors are anti-HBc^{+}. The risk is greatest for liver recipients compared with other organs and can be mitigated by vaccine immunity. Thus all nonimmune transplant candidates should be vaccinated. Various strategies to improve immunogenicity have been used, including higher dose, repeat vaccination, and altering

TABLE 308.15 Immunization Schedule in Transplant Recipients

VACCINE	TYPE OF VACCINE	ADMINISTRATION		ASSESSMENT OF SEROLOGIC RESPONSE TO VACCINE
		BEFORE TRANSPLANTATION	AFTER TRANSPLANTATION	
Influenza[a]	Nonlive	Yes	Yes	No
Hepatitis B[b]	Nonlive	Yes	Yes	Yes
Hepatitis A	Nonlive	Yes	Yes	Yes
Tetanus	Nonlive	Yes	Yes	No
Pertussis (Tdap)	Nonlive	Yes	Yes	No
Inactivated poliovirus vaccine	Nonlive	Yes	Yes	No
Streptococcus pneumoniae[c]	Nonlive	Yes	Yes	No
Neisseria meningitidis (MCV4)	Nonlive	Yes	Yes	No
Human papilloma virus	Nonlive	Yes	Yes	No
Mumps/measles/rubella	Live-attenuated	Yes	No	No
Varicella (live-attenuated; Varivax)[d]	Live-attenuated	Yes	No	Yes
Varicella (live-attenuated; Zostavax)[e]	Live-attenuated	Yes	No	No
Varicella (subunit; Shingrix)[f]	Nonlive	Yes	No existing guidelines	No

[a]Refers to inactivated influenza formulations. The live-attenuated influenza vaccine is contraindicated posttransplantation.
[b]Higher dose or coformulation (hepatitis A/B) might have enhanced immunogenicity.
[c]Sequential immunization with pneumococcal conjugated and polysaccharide vaccines is recommended (see text).
[d]For varicella-zoster virus (VZV)-seronegative patients, defer transplantation for 4 weeks after vaccination.
[e]For VZV-seropositive patients older than 60 years, defer transplantation for 4 weeks after vaccination.
[f]For VZV-seropositive patients older than 50 years.
Tdap, Tetanus, diphtheria, acellular pertussis vaccine.
Modified from Table 3 in Danziger-Isakov L, Kumar D; AST Infectious Diseases Community of Practice. Vaccination in solid organ transplantation. Am J Transplant. *2013;13(suppl 4):311–317.*

the route. Recently, a TLR-agonist adjuvanted HBV vaccine has been FDA approved in the United States but has not specifically been evaluated as a strategy to improve immunogenicity in transplant candidates or recipients.

Hepatitis C

Historical data had shown that use of organs from donors with HCV infection was associated with a high risk for HCV transmission and generally worse outcomes attributable to HCV,[257,258] but these studies were in an era of less effective and more toxic therapies. With the advent of newer therapies, and within the context of increased numbers of young donors with active HCV infection, several reports have reported the use of organs from HCV viremic donors for HCV-noninfected recipients. Various strategies, including treatment initiation after initial stabilization posttransplant, or "preemptive" initiation of therapy immediately posttransplant (even prior to documented transmitted infection in the recipient), have been reported to successfully treat HCV infection transmitted to the recipient.[257,258] Although the reported number of such transplants is small and the duration of follow-up relatively short, it represents a novel strategy to potentially safely increase the pool of available donors and organs.

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The complete reference list is available online at Expert Consult.

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309 Infections in Patients With Spinal Cord Injury

Rabih O. Darouiche

SHORT VIEW SUMMARY

Definition
- Spinal cord injury (SCI) results from mechanical compression, vascular insult, or both.

Prevalence and Etiology
- SCI affects almost 1 per 1000 persons.
- Causes of SCI include vehicular accidents, falls, violence, sports, and infection.
- Infection can cause or result from SCI.

URINARY TRACT INFECTION
- Urinary tract infection (UTI) is the most common infection and leading cause of repeated hospitalization.
- UTIs are mostly caused by usual bowel microbiota (gram-negative bacteria and enterococci).
- Intermittent catheterization is preferred to indwelling bladder catheters.
- Preventive approaches are still not very effective.
- Failure to distinguish between clinical UTI and asymptomatic pyuria frequently results in unnecessary therapy.

PNEUMONIA
- Pneumonia has the highest infection-related mortality.
- It occurs mostly in patients with tetraplegia.
- Community-acquired and hospital-acquired microbes are comparable to those found in the general population.

INFECTION OF PRESSURE SORES AND BONE
- This diagnosis is very problematic.
- The broadest microbial etiology includes gram-positive cocci, gram-negative bacilli, and anaerobes.
- Multidisciplinary management requires long and repeated hospital stays.

MULTIRESISTANT ORGANISMS IN SPINAL CORD INJURY UNITS
- Multiresistant organisms include methicillin-resistant *Staphylococcus aureus,* vancomycin-resistant *Enterococcus,* gram-negative bacteria, and *Clostridioides difficile* (formerly *Clostridium difficile*).
- These organisms are more prevalent in SCI units than in general hospital wards.
- Proper infection control measures may reduce both colonization and infection and can delay the onset of complications, but ultimately may replace organisms with others.

Spinal cord injury (SCI) is a devastating condition that is unique in terms of its multisystem impact and need for multidisciplinary management. Moreover, the prevalence and occurrence of SCI have continued to escalate over the years. In 2017, approximately 285,000 Americans experienced the consequences of SCI, and at least 17,500 new cases of SCI accrue each year in the United States.[1] Although motor vehicle crash is the most frequent overall cause of SCI,[1] the most common infectious cause is spinal epidural abscess,[2] the incidence of which continues to escalate.[3] Not only can infection cause SCI, but also infection frequently occurs subsequent to the injury and can result in major morbidity and mortality.

Because SCI primarily affects young adults, patients experience acute, chronic, and recurrent infections. Most infections that occur in patients with SCI also affect able-bodied patients, but the frequency and clinical characteristics of infections vary between these populations. Although urinary tract infection (UTI) is the most common type of infection and the leading cause for rehospitalization, pneumonia has the highest infection-related mortality, and infections of pressure sores and underlying bone are the most difficult to manage. Although patients with SCI are particularly predisposed to infection in the acute setting of the injury, most infections occur much later in this population. In this chapter, discussion focuses on the factors that predispose to infection, the challenges in evaluating patients for infection, the most prominent infections in this population, and multiresistant organisms in the SCI setting.

FACTORS THAT PREDISPOSE TO INFECTION

Risks for infection in patients with SCI can be either systemic or organ related. As SCI does not, in and by itself, depress general host immunity, uninfected individuals with SCI usually have normal function of T and B lymphocytes. However, elevated levels of circulating proinflammatory cytokines and autoantibodies are present in the serum of patients with SCI without medical complications and are further elevated in such patients with neuropathic pain, UTI, or pressure ulcers relative to healthy, able-bodied individuals. Compared with able-bodied cohorts, patients with SCI, particularly individuals with tetraplegia, usually have higher levels of inflammatory markers such as C-reactive protein and cytokines (e.g., interleukin-6 and tumor necrosis factor-α), and this difference can be attributed to undetected inflammation or occult infection. Receipt of high-dose glucocorticosteroids in the acute setting of SCI and chronic complicating conditions (including stress, malnutrition, and renal failure) can impair the immune responses to infection. An animal model showed decreased local inflammatory markers in the bladder tissue of mice with SCI during infection and a delayed antiinflammatory response after being treated, which may contribute to the increased risk of UTI and the chronic inflammation that can persist after treatment.

More importantly, patients with SCI possess unique organ-related factors that predispose them to infection. For instance, most patients have a neurogenic bladder and have frequent episodes of UTI attributed to urinary stasis and bladder catheterization. Urinary stasis greatly impairs the naturally protective mechanisms of the urinary tract, including the washout effect of voiding and phagocytic capacity of bladder epithelial cells. Although some techniques of bladder catheterization are safer than others, none can be carried out without the potential risk for introducing organisms into the urinary tract. Both paralytic ileus and abnormal state of consciousness caused by associated head injury or illicit drug ingestion or both can predispose to aspiration pneumonia in the acute stage of SCI. In individuals with cervical or high thoracic cord lesions, weakness of the diaphragmatic and intercostal muscles impairs the capacity to clear respiratory secretions. Skin breakdown in anesthetic areas, immobility, disuse-induced muscle atrophy, urinary leakage, and fecal contamination predispose to infection of pressure sores.

Frequent insertion of urologic, vascular, orthopedic, respiratory, gastrointestinal, and neurosurgical devices in patients with SCI predisposes to various prosthesis-related infections. This helps explain why

hospital-acquired infections most commonly affect the urinary tract, bloodstream, and musculoskeletal system. Patients with SCI generally have a higher rate of hospital-acquired infections than other groups of patients. About one-third of patients with SCI develop infection during hospitalization, with an overall incidence of 35 episodes of hospital-acquired infections per 1000 hospital-days.[4-6]

CHALLENGES IN EVALUATING PATIENTS FOR INFECTION

A number of unique challenges can be encountered when attempting to establish diagnosis and provide treatment of infections in patients with SCI (Table 309.1). Infection often manifests differently in patients with SCI compared with able-bodied individuals. Altered or absent sensations are the most important impediment to the diagnosis of infection. Although dysuria, frequency, and urgency are regularly present in able-bodied patients with UTI, these symptoms rarely exist in infected patients with SCI. The diagnosis of perinephric abscess is particularly challenging in patients with high sensory level lesions who do not appreciate flank pain or tenderness. The inability to recognize the signs and symptoms of cord damage contributes to the delay in diagnosing spinal epidural abscess below the level of injury. The diagnostic dilemma caused by the paucity of clinical findings can be heightened by the presence of neurogenic or referred pain that may not be related to the infection. Furthermore, multiple infections can occur concurrently in 20% of patients with SCI. Even more problematic than identifying the source of an infection is discerning whether fever is caused by an infection or a noninfectious condition that may closely mimic infection and cause almost one-fifth of episodes of fever in these patients.

A diagnostic conundrum may arise when unique thermoregulatory and autonomic disturbances cause fever in patients with SCI. Because of the imbalance between heat production and heat loss, patients with an injury to the spinal cord above T8 may not be able to maintain a normal body temperature in response to heating or cooling (poikilothermia). This phenomenon of altered thermoregulation is attributed to the loss of sweating and muscular activity below the spinal cord lesion. These factors may contribute to the occurrence of self-limited febrile episodes in patients with SCI that resolve spontaneously within hours to days. However, neither alterations in environmental temperature nor changes in a subject's sweating and muscular activity may explain the occurrence of prolonged fever in recently injured quadriplegic patients who have no identifiable focus of infection. This unique syndrome—so-called quadriplegia fever—lasts weeks to months and is problematic because it may incite repeated evaluation for infection and multiple courses of antibiotics, but to no avail. Rarely, fever may occur in the context of autonomic dysreflexia, a paroxysmal syndrome characterized mainly by hypertension, sweating, facial flushing, and headache. Occasionally, bradycardia may also be present and can help differentiate febrile episodes of autonomic dysreflexia from infection. This type of autonomic hyperactivity is seen only in patients with SCI above T6 and is usually triggered by distention of viscera (bladder and rectum), cutaneous stimulation (e.g., ingrown toenails), or even infection.

Treatment of infection in patients with SCI also poses special challenges. For example, two opposing factors resulting from changes in body composition after SCI can alter the disposition of certain systemically administered antibiotics such as vancomycin and aminoglycosides. On one hand, patients with SCI have expanded extracellular volume attributed to retention of extracellular water as subclinical edema and replacement of diminished skeletal muscle mass by extracellular water. As a result, these patients have a larger weight-adjusted volume of distribution of drugs and may require larger weight-adjusted loading and maintenance doses than able-bodied counterparts to achieve similar antibiotic concentrations. On the other hand, this potential effect on antibiotic concentration can be counteracted, at least in part, by the frequent overestimation of creatinine clearance when using current formulas that were originally devised for able-bodied individuals to predict creatinine clearance in patients with chronic SCI who have low serum creatinine levels. A proper 24-hour collection of urine can accurately estimate renal function. The multiple complicated conditions of patients with SCI result in frequent rehospitalization.[7-9]

TABLE 309.1 Challenges in Evaluating Infection in Spinal Cord–Injured Patients

General Factors
Altered or absent sensations
Interference of neurogenic pain with localization of the source of infection
Coexistence of multiple infections
Mimicry of infection by noninfectious conditions
Thermoregulatory and autonomic disturbances
Need for adjusting doses of antibiotics such as vancomycin and aminoglycosides
Infection-Specific Factors
Urinary Tract Infection
Almost universal prevalence of bacteriuria
Level of pyuria as indicator of infection
Nonspecific manifestations of symptomatic infection
Relevance of urine cultures growing several bacterial organisms
Pneumonia
Impact of ineffective cough on determining microbial cause
Defective perception of dyspnea and need to evaluate gas exchange
Eligibility for and efficacy of immunization
Infection of Pressure Sores
Limitations of history provided by patient
High importance of physical findings in diagnosing ulcer infection
Universal bacterial colonization of pressure sores and unreliability of swab cultures
Potential reason for failure to respond to therapy
Deceptive appearance of sinus tract
Osteomyelitis
Relevance of cultured samples
Possible variations of findings from bones beneath different sores
Significance of organisms growing from cultures of bone
Poor predictive value of clinical evaluation for osteomyelitis
Appropriateness of imaging studies for diagnosis and follow-up

URINARY TRACT INFECTION

UTIs are the most common type of infection in patients with both traumatic and nontraumatic SCI and occur at a rate of 2.5 episodes per patient per year. In general, inadequate antibiotics are available with increasing costs of treatment of UTI of about $2 billion a year in the United States. In patients with chronic indwelling bladder catheters (transurethral or suprapubic), bacteriuria is almost universal and occurs at a higher rate than in patients with intermittent bladder catheterization (98% vs. 70%). A longer interval between intermittent bladder catheterizations may be associated with a higher incidence of bacteriuria. Although outpatients may find it more practical to use clean reusable rather than sterile catheters for intermittent bladder catheterization, there is conflicting evidence regarding the value of clean versus sterile bladder catheterization.

Asymptomatic bladder colonization may progress to symptomatic UTI but often does not. Typical manifestations of UTI (including dysuria, urgency, frequency, suprapubic discomfort, and, in patients with pyelonephritis, costovertebral angle tenderness) are rarely present in patients with SCI. Instead, change in voiding habits, increase in the residual volume of urine in the bladder, foul-smelling urine, worsening of muscular spasticity, and aggravation of autonomic dysreflexia are often the only clinical clues to the presence of UTI. Because of the nonspecificity of these clinical manifestations, other causes should be excluded before diagnosing UTI. Although the lack of pyuria reasonably predicts the absence of UTI in patients with SCI, pyuria is a nonspecific finding that is also observed in uninfected individuals whose urinary tract is inflamed by catheter manipulations, renal calculi, and interstitial nephritis. Other commonly reported abnormal laboratory findings in the urine, including nitrite and leukocyte esterase, are also not specific for infection. Another diagnostic limitation is that about two-fifths of patients with SCI incorrectly attribute their bouts of illness to UTI. As with other patient populations who require bladder catheterization, bacterial concentration in urine of patients with SCI may not help differentiate between asymptomatic bladder colonization and symptomatic UTI. Most cases of UTI in patients with SCI are caused by commensal

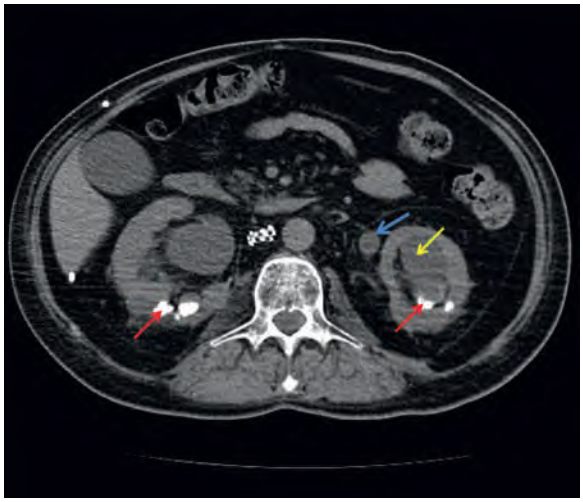

FIG. 309.1 Unenhanced computed tomography scan of the abdomen in a spinal cord–injured patient with a chronic indwelling bladder catheter and repeated episodes of upper and lower urinary tract infection due to *Proteus mirabilis*. Note bilateral kidney stones *(red arrows)*, left hydronephrosis *(yellow arrow)*, and left hydroureter *(blue arrow)*.

organisms of the bowel and perineum, particularly gram-negative bacilli and enterococci. The patient's sex and level of injury may affect the microbiology of organisms residing in the bladder. The finding of polymicrobial bacteriuria is particularly problematic in patients with SCI. Almost half of positive urine cultures in these patients grow more than one organism, and polymicrobial bacteriuria can be more prevalent in patients who have chronic indwelling urethral catheters. Although isolation of multiple bacterial species in the general population is often viewed as indicative of contamination, a similar finding in catheterized patients with SCI should not be disregarded. Isolation of several uropathogens can be associated with a UTI episode that fails to respond to antibiotic therapy directed against only one or some of the organisms but is eradicated after providing additional antimicrobial coverage against other isolated organisms. Although most urine cultures are obtained from patients with lower UTI only and in whom the yield of blood cultures is extremely low, the detection of concurrent bacteremia confirms the pathogenicity of organisms isolated from urine culture. Even in patients who have pyelonephritis in association with polymicrobial bacteriuria, isolation of only one organism from blood cultures may not negate the role of other bacteria in causing UTI. Because it is difficult to differentiate accurately between cultured organisms causing infection and asymptomatic colonizers, it may be reasonable to treat all potentially pathogenic organisms grown from urine cultures in patients with a diagnosis of infection.

A preventive approach that dramatically protects against UTI has not been identified since the advent of closed urinary drainage almost a half-century ago. Optimizing urinary drainage and switching, whenever feasible, from an indwelling bladder catheter to intermittent bladder catheterization or even external condom-based drainage, remain the cornerstone of prevention. The incidence of bladder stones, a condition associated with repeated bouts of UTI, is higher in patients who rely on indwelling versus intermittent bladder catheterization.[10] Fig. 309.1 delineates the relationship between renal calculi, urinary tract obstruction, and infection. Upper tract urolithiasis is commonly managed with extracorporeal shock wave lithotripsy or percutaneous nephrolithotomy.

A number of approaches have been examined for their potential protection against infection. Although clinical data exist regarding the ability of antimicrobial-modified catheters (including hydrogel/silver-coated and nitrofurantoin-coated) and intermittent bladder catheters to reduce the rate of bacteriuria (not clinical UTI) in the general population, there is no strong evidence that such catheters can prevent or reduce clinical UTI. However, both a randomized controlled trial and a single-arm study reported that patients who received injection of botulinum toxin A into the detrusor muscle experienced about 45% reduction in the incidence of UTI compared with the preinjection period.[11–13] Because botulinum toxin A reduces the detrusor pressure, it could help prevent reflux and therefore pyelonephritis.[14] The coating of silicone with mannoside-poly(amido amine) decreases biofilm formation.[15] Furthermore, a number of studies focused on the use of *Escherichia coli* strain 83972 to prevent UTI in patients with neurogenic bladder.[16–18]

Asymptomatic bacteriuria can progress to symptomatic infection, and thus several approaches have been designed to prevent or eradicate asymptomatic bacteriuria.[19] However, there were no significant differences in outcomes between high-dose and low-dose antibiotics given before endoscopic urologic procedures.[20]

PNEUMONIA

Although much less frequent than UTI, pneumonia is the most common cause of death related to infection, at a rate of 30% to 35% in patients with SCI. Pulmonary complications in the immediate postinjury period are particularly likely to occur in the first few months after cervical or high thoracic SCI in quadriplegics and older adults.[21–26] Pneumonia in acutely injured patients is associated with prolonged length of stay and escalated hospital costs. Patients with cervical SCI and swallowing problems leading to aspiration may benefit from having a percutaneous feeding tube. Aspiration pneumonia is usually caused by gram-negative or anaerobic bacteria. As is the case in able-bodied persons, community-acquired bacterial pneumonia in patients with SCI is mostly caused by *Streptococcus pneumoniae, Haemophilus influenzae,* and *Branhamella catarrhalis. Pseudomonas aeruginosa,* methicillin-resistant *Staphylococcus aureus* (MRSA), and *Acinetobacter baumannii* are the three most common causes of ventilator-associated pneumonia, which can be polymicrobial in about one-fourth of infected cases. Because of defective sensation of respiratory muscle fatigue and altered perceptions of dyspnea, pneumonia in patients with SCI may progress to respiratory failure in an unpredictable fashion. Therefore, evaluation of gas exchange, preferably by analysis of arterial blood gases, is strongly recommended when treating pneumonia. Transcutaneous measurement of oxygen saturation also may be used, but caution is needed because heated electrodes can burn the insensate skin.

A number of noninfectious conditions can clinically mimic pneumonia. For example, atelectasis, similar to pneumonia, commonly occurs because of retained pulmonary secretions early after injury to the cervical or high thoracic cord. Because patients may have altered or absent sensations of chest pain or dyspnea and ineffective cough, the only clinical clues that suggest the diagnosis of pneumonia may be tachypnea, tachycardia, fever, and leukocytosis. However, atelectasis may also be accompanied by an element of low-grade fever and leukocytosis. The site of pulmonary involvement may not help differentiate atelectasis from pneumonia because both conditions predominantly involve the left lung, owing to difficulty in suctioning the left main stem bronchus that branches off at a more acute angle than the right bronchus. In such cases, bronchoscopy may be required for diagnostic and therapeutic purposes.

Another condition that can be clinically confused with pneumonia is pulmonary embolism, which occurs in about 5% of patients with SCI, frequently without an identifiable thrombotic source. Although pulmonary embolism can ordinarily be diagnosed by a ventilation-perfusion lung scan, the observed defects on scanning may be difficult to interpret in patients who also have atelectasis; a pulmonary angiogram may be required for definitive diagnosis in such cases. A negative D dimer test in the blood would reasonably rule out pulmonary embolism in this setting. In the acute stage of SCI, associated fracture of a long bone can lead to fat embolism, which may or may not manifest as the clinical stigmata of petechiae and cerebral dysfunction. Aspiration of gastric contents in the presence of paralytic ileus and an ineffective cough reflex can lead to chemical pneumonitis that mimics bacterial pneumonia; evaluation of an adequate sample of respiratory secretions may help differentiate between these two clinical entities. Finally, pulmonary contusion can be mistaken for pneumonia in the acute setting of SCI. Because pneumonia qualifies as an independent risk factor for poor neurologic recovery after complete acute SCI, it is imperative to accurately and quickly diagnose and treat pneumonia.

Because patients with SCI are at a greater risk for developing pneumonia than able-bodied persons, it is important to assess the

immunization status in such patients. By virtue of age (>50 years), chronic respiratory disease, residence in chronic-care facilities, or all of these factors, almost two-thirds of patients with SCI are eligible for vaccination against *S. pneumoniae* and influenza viruses. The antibody response to pneumococcal and influenza vaccination of patients with SCI is adequate. Education and reminders escalate rates of vaccination in these patients. Notwithstanding the lack of studies that examine the clinical benefit of these vaccinations in this population, it may be justifiable to administer pneumococcal and influenza vaccines to all patients with SCI.

Pneumonia in patients with SCI is usually treated with a 10- to 14-day course of antibiotic therapy. In the absence of aspiration or respiratory devices, a quinolone or a combination of a macrolide and cephalosporin is adequate for empirical treatment of community-acquired respiratory infections. Coverage for anaerobes, gram-negative bacteria, and MRSA is required for therapy for hospital-acquired aspiration pneumonia. Agents active against MRSA and *P. aeruginosa* should be empirically considered in patients with infections associated with respiratory devices. The reported observation that most antibiotics prescribed for acute respiratory conditions in patients with SCI are considered unnecessary underscores the essential role of education in preventing antibiotic abuse.

INFECTION OF PRESSURE SORES

Local factors that contribute to infection of pressure sores include breaks in the integrity of the skin barrier, pressure-induced changes, and contamination from contiguous dirty areas.[27–29] Accordingly, pressure sores frequently become infected with staphylococci, streptococci, and gram-negative or anaerobic bacteria. Most pressure sores in patients with SCI develop in areas adjacent to the ischium, sacrum, and greater trochanter. In paralyzed individuals who cannot directly visualize the ulcers, their history is usually incomplete, and the infection is already advanced by the time they seek medical care. Patients with grade 3 or 4 SCI are more likely than the general population to develop Fournier gangrene, which is the most fearsome form of necrotizing fasciitis that affects the perineal and genital regions and usually results from polymicrobial infection. Because of inadequate sensations, physical findings (fever; purulent drainage; and surrounding inflammatory changes including erythema, swelling, and warmth) are usually relied on to diagnose infection.

Because pressure sores are universally colonized by bacteria, samples for culture should not be obtained unless infection is clinically evident. In patients with seemingly infected pressure ulcers, biopsy of deep tissue is the most reliable means for identifying the infecting pathogen. Cultures of swab specimens from an ulcer or a sinus tract are generally unreliable and often misleading, leading to overtreatment of colonizing antibiotic-resistant bacteria, and cultures of material obtained by needle aspiration tend to overestimate the number of bacterial isolates. If cellulitis is recognized adjacent to a decubitus ulcer, the challenge to the clinician is to discern the infecting organism. Biopsy of deep soft tissue is a reliable means for determining the microbiologic cause of infection.

A combined medical-surgical approach is often required to establish cure of infection. The potential benefit of applying negative pressure to deep pressure ulcers by using a vacuum-assisted closure device is still unknown. Surgery is done to débride nonviable tissue and drain infected material. A lack of response of infected ulcers to therapy may be the result of inadequate antibiotic therapy targeted to the wrong organisms, undrained abscess, communication of the ulcer with an infected bone or joint, or a fistula communicating with the gastrointestinal or urinary tract. The appearance of newly isolated bacterial species soon after initiating antibiotic therapy probably indicates colonization; unless there has been an initial response followed by recurrence of fever, these organisms should generally be ignored. Even in patients with apparently healed ulcers, deep soft tissue abscesses may exist, sometimes causing fever or even bacteremia.

Although the sensitivity of nuclear scintigraphy for detecting soft tissue abscesses is generally very high, this test can also yield positive results in patients with SCI who have an infected pressure sore without an associated abscess. Soft tissue abscess in association with an infected sore can be more accurately diagnosed by computed tomography (CT) or magnetic resonance imaging (MRI) than by nuclear scintigraphy. Because pressure necrosis affects subcutaneous tissues and muscles more than the skin, the opening of a sinus tract onto the skin may appear deceptively small. Although potentially helpful, probing may not reveal the full depth of the tract. Sinography can delineate the full depth of the tract and the potential communication with bone, joint, intra-abdominal abscess, or visceral organs. Injection of dye into the intestines or bladder may also help detect a fistulous connection.

OSTEOMYELITIS

Most cases of osteomyelitis in patients with SCI occur beneath pressure sores.[30–34] Less common forms include prosthesis-related, postoperative, hematogenous, and vertebral osteomyelitis. In general, it is difficult to determine whether bone beneath a decubitus ulcer is infected and, if infected, by which organism. Not only are cultures of a swab specimen from the ulcer of little value in predicting the causative pathogen of osteomyelitis, but they also can provide deceptive information that leads to improper antibiotic treatment. The definitive diagnosis of osteomyelitis beneath pressure sores requires histopathologic examination of bone tissue. Histopathologic examination of bone specimens obtained by percutaneous needle biopsy demonstrates osteomyelitis beneath about one-fifth to one-third of pressure sores. Because osteomyelitis is likely to be a focal process and percutaneous bone biopsy may fail to sample the truly infected focus, bone infection is more accurately diagnosed by intraoperative bone biopsy. As seen in Fig. 309.2, ischial pressure sores may result in infection of both muscle and bone. In patients with multiple pressure ulcers, histopathologic evaluation of a bone specimen from one site may not necessarily reflect the same findings beneath the other ulcers. In addition, even if pathologic findings are similar, bone cultures from various sites may grow different organisms.

Because of the high frequency of bacterial colonization of fibrotic tissue adherent to bone, cultures of bone specimens are positive in most patients in whom histopathologic examination of bone tissue is not compatible with osteomyelitis. Moreover, quantitative bone cultures do not differentiate osteomyelitis from colonization or infection of overlying soft tissue. Therefore, the diagnosis of osteomyelitis should be made by positive histopathologic findings, in which case culture results would be relied on to manage antibiotic treatment against grown organisms except the usual colonizers such as *Staphylococcus epidermidis* and diphtheroids. Most cases of osteomyelitis beneath pressure sores are caused by two or more bacterial species, including gram-positive cocci (mainly *S. aureus* and streptococci), gram-negative bacilli (including *P. aeruginosa* and Enterobacteriaceae), anaerobes (particularly *Bacteroides* and *Fusobacterium* spp.), and, rarely, *Candida* spp.

Clinical evaluation poorly predicts the presence of osteomyelitis beneath nonhealing deep pressure sores. In particular, clinical information

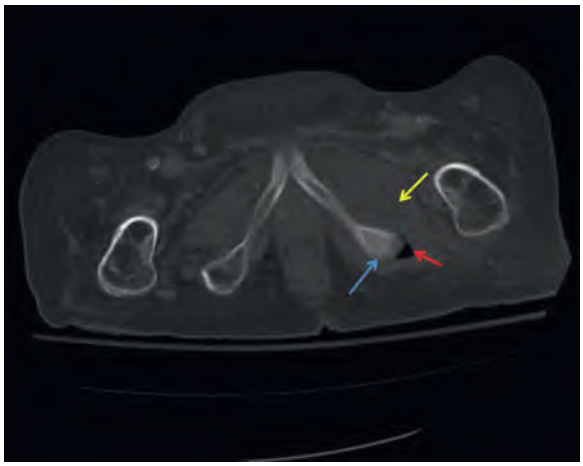

FIG. 309.2 Contrast-enhanced computed tomography scan of the pelvis in a spinal cord–injured patient with an unhealed ischial pressure sore. Note the presence of chronic osteomyelitis *(blue arrow)*, inflamed muscle *(yellow arrow)*, and soft tissue defect *(red arrow)*.

(duration of ulcer, bone exposure, purulent drainage, fever), laboratory data (including leukocytosis and rising erythrocyte sedimentation rate and C-reactive protein), and radiologic findings (plain radiographs and technetium bone scintiscans) do not correlate well with histopathologic findings. Nuclear scintiscans are highly sensitive but poorly specific for diagnosing osteomyelitis beneath pressure sores. This low specificity is attributed to the capacity of the injected technetium to concentrate in areas of bone that have pressure-induced changes or heterotopic ossification. The most desired finding of a bone scintiscan is a negative result, which would almost completely exclude the diagnosis of osteomyelitis beneath pressure sores and obviate the need for bone biopsy. Both CT and MRI can identify osteomyelitis as the cause of nonhealing pressure ulcers.

Although failure of pressure ulcers to heal can result from underlying osteomyelitis, it is more likely to result from noninfectious causes, such as pressure-related changes, spasticity, malnutrition, and heterotopic bone ossification. The last-mentioned entity can mimic osteomyelitis both clinically and radiologically. Heterotopic bone ossification evolves in up to half of all patients with SCI, particularly in the first year after injury among patients who are completely paralyzed or have pressure sores. It can cause warm erythematous swelling of soft tissues, primarily in areas adjacent to the hip and knee. Although serum alkaline phosphatase level can be elevated early, it is not diagnostic of heterotopic bone ossification because many other proliferative bone processes may also cause an abnormal elevation. Radiographic changes are often absent for 1 to 2 weeks after clinical signs appear, but by then a technetium bone scintiscan should reveal increased uptake.

Patients with SCI who have osteomyelitis beneath pressure sores are usually treated with antibiotics and, when indicated, surgical débridement. Although the ideal duration of antibiotic therapy is not clear, most patients receive at least 4 to 6 weeks of antibiotic therapy. No evidence exists to determine whether the duration of antibiotic therapy of vertebral osteomyelitis should be different between patients with SCI versus patients without SCI. Although parenteral antibiotics have traditionally been used, oral administration of highly bioavailable drugs may be considered. Musculocutaneous flap surgery is preferable to débridement alone because the transposition of a well-vascularized muscle allows more extensive removal of devitalized tissue, enhances host defense against infection, and provides a better vascular supply to facilitate bone healing. Patients with improperly treated osteomyelitis may develop deep abscesses and a sinus tract after reconstructive surgery. In patients with recurrent infection or very extensive disease, hemipelvectomy may be considered. Changes on plain radiographs and bone scintiscans may persist after what clinically seems to be successful treatment of osteomyelitis.

BLOODSTREAM INFECTION

Infections of the urinary tract, pressure sores, lungs, and vascular access are the most common identifiable sources of bloodstream infection in patients with SCI.[35–39] An occult deep-seated abscess may be the culprit in bacteremic patients without an apparent source. Bloodstream infections associated with UTI and long-term hemodialysis access are mostly caused by gram-negative bacilli, whereas staphylococci are the most frequent isolates from blood cultures in patients with infection of pressure sores or short-term vascular access. Because vascular catheter-related bloodstream infection is severalfold more likely to be caused by gram-negative bacteria in patients with SCI than in the general population, coverage against gram-negative bacteria should be considered when initiating empirical antibiotic therapy. This recommendation is supported by the reported observation that more than one-third of patients received inadequate empirical treatment, which occurred mostly in patients with polymicrobial bloodstream infection.

INTRAABDOMINAL INFECTION

Because cholelithiasis is more common in patients with SCI than in the general population, biliary infections are the most frequent intraabdominal infections in this population. Although most gallstones may remain asymptomatic, some result in cholecystitis or migrate down the common bile duct to cause cholangitis or pancreatitis. A ruptured viscus or, less commonly, a fistulous connection with a pressure sore can result in the formation of intraabdominal abscesses. Intraabdominal infections may be misdiagnosed, particularly in patients with high cord lesions, because they frequently manifest as abdominal distention, diffuse spasm of abdominal wall musculature, and rigidity on palpation but no localized abdominal pain or tenderness.[40] Ultrasonography, CT, and MRI of the abdomen all are useful modalities to identify an occult abscess.

MULTIRESISTANT ORGANISMS IN THE SPINAL CORD INJURY SETTING

Multiresistant bacteria that have a predilection to exist in SCI units more than in general hospital wards include MRSA (the most common multiresistant organism), vancomycin-resistant *Enterococcus* (VRE), and gram-negative bacilli that produce extended-spectrum β-lactamase or belong to the carbapenem-resistant Enterobacteriaceae.[41–45] Roommate contacts of patients colonized or infected by any of these multiresistant bacteria are at increased risk for acquiring those organisms. As is the case with able-bodied persons, the occurrence of carbapenem-resistant Enterobacteriaceae has also escalated in patients with spinal cord injury. Moreover, antibiotic resistance in SCI has continued to escalate. This has prompted the increasing use, albeit still relatively small, of a group of antibiotics that contain β-lactamase inhibitors. The role of intravesical *E. coli* bacteriophage treatment in patients with SCI has not been established for uropathogens.

Universal surveillance, contact precautions, hand hygiene, strict adherence to infection control practices, and an institutional culture change can blunt the spread and reduce MRSA health care–acquired infections in SCI units. In contrast to MRSA, which can exist in almost every body organ, VRE is cultured mostly from the urine, particularly in catheter-dependent patients. Although most episodes of growth of VRE from urine cultures represent asymptomatic bacteriuria and do not require antibiotic treatment, VRE colonization and residence in a long-term facility increase the risk for subsequent bacteremia. Catheter-dependent patients with SCI are predisposed to develop UTI caused by extended-spectrum β-lactamase–producing multiresistant gram-negative bacilli such as *E. coli* and *Klebsiella pneumoniae*. A potentially bigger menace to vulnerable patients with SCI would be the expanding presence of carbapenem-resistant Enterobacteriaceae. As mentioned, over many years, antibiotic resistance has escalated in SCI units. The recent availability of new antibiotics that include β-lactamase inhibitors can be helpful if these antibiotics are used properly.

Clostridioides difficile (Formerly *Clostridium difficile*)

Frequent administration of antibiotics and potentially suboptimal hygienic practices in SCI units help explain the relatively high prevalence of *Clostridioides difficile* infection. In patients with neurogenic bowel and defective sensation, *C. difficile*–associated gastrointestinal disease can remain clinically undetected until a catastrophe such as toxic megacolon or bowel perforation evolves. Patients with SCI are more likely to have prolonged or recurrent *C. difficile* infections. Additionally, the clinical presentation with diarrhea may not be interpreted as infection versus neurologically related gastrointestinal dysfunction. Physicians should have a high index of suspicion, especially in patients with SCI who receive prolonged or multiple antibiotics.

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310 Infections in Older Adults

Kevin P. High

SHORT VIEW SUMMARY

- Older adults are more likely to experience infection and severe infection than young adults due to accumulation of comorbid illnesses, reduced functional status (physical, cognitive, sensory), place of residence (e.g., nursing home), declining immunity with advancing age (immune senescence) and physiologic changes that accompany age (e.g., reduced stomach acid, gag/cough reflexes).
- Seniors are less likely to present with classic symptoms, even in the face of serious infection. Basal temperature is lower with advanced age, making fever less common; cognitive impairment and other comorbid illness may mask symptoms; and certain diagnostic tests, such as transthoracic echocardiography, are less sensitive in older adults.
- Antibiotic selection is rarely changed by age, but drug interactions and the need for dose alterations are more common with age. The first dose of antibiotic should be given as soon as possible and at full dose—do not "start low and go slow" —because rapid, effective treatment is more important in older adults, who have less physiologic reserve and delayed immune responses.
- Age and comorbidity influence a number of infectious syndromes: pneumonia, urinary tract infection, bacteremia/sepsis, endocarditis, bone/joint infection, and gastrointestinal infection. In general, the microbiologic differential diagnosis is broader in seniors, including an increase in multidrug-resistant organisms, especially in nursing home residents.
- Aging with human immunodeficiency virus (HIV), even well-treated and controlled infection, is associated with increased risk of comorbid illnesses (vs. those aging without HIV), including cardiovascular disease, hypertension, diabetes mellitus, bone fractures, cognitive impairment and dementia, cancer, kidney and liver disease, and even geriatric syndromes (frailty, falls, social isolation).
- Immunization is an important prevention strategy in seniors with specific age-related recommendations for pneumococcal vaccines, influenza vaccine formulations, and zoster vaccine. Advancing age, beginning even in the fourth decade, is associated with reduced responses to human papilloma virus and hepatitis vaccines. Yellow fever vaccine poses a much higher risk for adverse events in older adults, especially those older than 70 years.

PREDISPOSITION OF OLDER ADULTS TO INFECTION

Risk factors for infection in older adults are numerous and often coexist in complex relationships. Seemingly similar patients by conventional criteria may have very different risk due to measures not often used in young adults. These include comorbid illness, polypharmacy, functional status (physical, cognitive, sensory), place of residence, and individual variations in physiologic changes that accompany age (e.g., declining glomerular filtration rate, reduced gag/cough reflexes).

Comorbid Illness

The most important cofactor for infection in older adults is the accumulation of comorbid disease with age. Many infectious diseases are a direct or indirect result of chronic comorbid conditions (e.g., diabetes mellitus, renal failure, chronic pulmonary disease, edema, immobility). These comorbidities most often result in reduced local innate immunity. For example, chronic obstructive pulmonary disease (COPD) is associated with impaired mucociliary clearance, alveolar macrophage dysfunction, and suppressed cough mechanism, substantially increasing the risk for lower respiratory tract infection in older adults with COPD.

Comorbid diseases in older adults with infection can also be important predictors for worse outcomes—more important than age itself. In patients with community-acquired pneumonia (CAP), multiple comorbid conditions and advanced age greatly increase the risk of mortality. Age itself dominates many CAP prognostic scoring algorithms, but age alone is not a strong predictor of mortality once patients exceed 75 years of age; in patients at the extreme of older age, comorbidity dominates, not age itself. Furthermore, cognitive decline and other barriers that delay diagnosis or reduce adherence to medical regimens often necessitate hospitalization of older adults in circumstances where their younger counterparts can be treated as outpatients, further increasing costs and enhancing the rate of complications.

Waning Immunity With Age (Immune Senescence)

Although comorbidities substantially predispose older adults to infection, there is an underlying waning of immune responses that accompany old age even in the absence of comorbidity; this is called immune senescence. Immune senescence is not merely a global state of reduced immunity but a dysregulation of immune responses at multiple levels. A complete review of immune senescence is beyond the scope of this chapter, but both innate and adaptive responses are significantly dysregulated.

Innate immune responses are *increased* in some respects, but *decreased* in others.[1] Critical innate immune components that decline with age include physical barriers such as skin integrity, cough/gag reflex, mucociliary clearance, and gastric acid. Innate immune responses are also dysregulated at the cellular level, with impaired polymorphonuclear neutrophil function and dysregulation of inflammatory responses triggered by pathogen-associated molecular patterns via Toll-like receptors (Fig. 310.1). Despite impaired stimulus-triggered responses, there is often a chronic, low-level inflammation present in older adults. The cause(s) of this low-level inflammation are not well elucidated, but it likely plays a role in chronic disease development (e.g., vascular inflammation) and inhibitory mechanisms engaged to keep this low-level inflammation in check may be a cause, in part, of the slower innate response to infection seen in older adults.

In the adaptive immune system there are decreases in naïve T-cell subsets, with accumulation of memory T cells, substantially reduced diversity of the overall T-cell pool, and impaired responses to specific antigen (Fig. 310.2).[2]

Although there is little doubt that immune senescence exists, the clinical role of this phenomenon in the predisposition of older adults to clinical infection is poorly defined. Immune senescence markers have been extensively studied in vaccine responses measured most often by antibody titers and other surrogate markers, but only a few studies

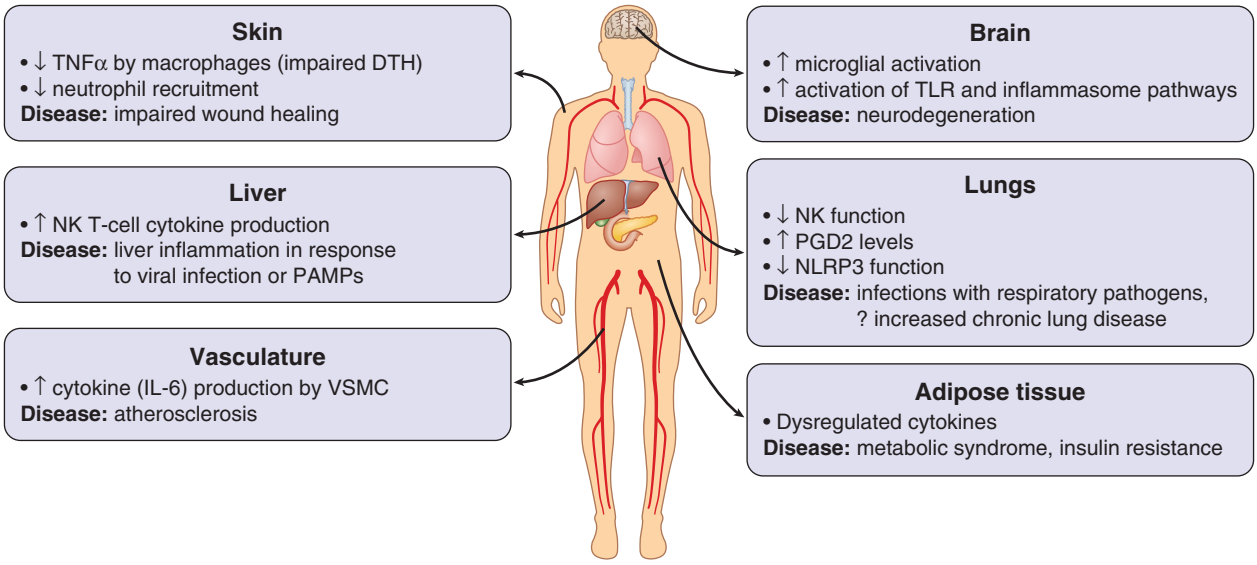


FIG. 310.1 **Innate immune changes with aging and consequences in specific organ systems.** *DTH,* Delayed-type hypersensitivity (response); *IL-6,* interleukin-6; *NK,* natural killer; *NLRP3,* NLR family pyrin domain containing 3; *PAMPs,* pathogen-associated molecular patterns; *PGD2,* prostaglandin D2; *TNF-α,* tumor necrosis factor-α; *VSMC,* vascular smooth muscle cell. *(Reprinted with permission from Shaw AC, Goldstein DR, Montgomery RR. Age-dependent dysregulation of innate immunity.* Nat Rev Immunol. *2013;13:875–887.)*

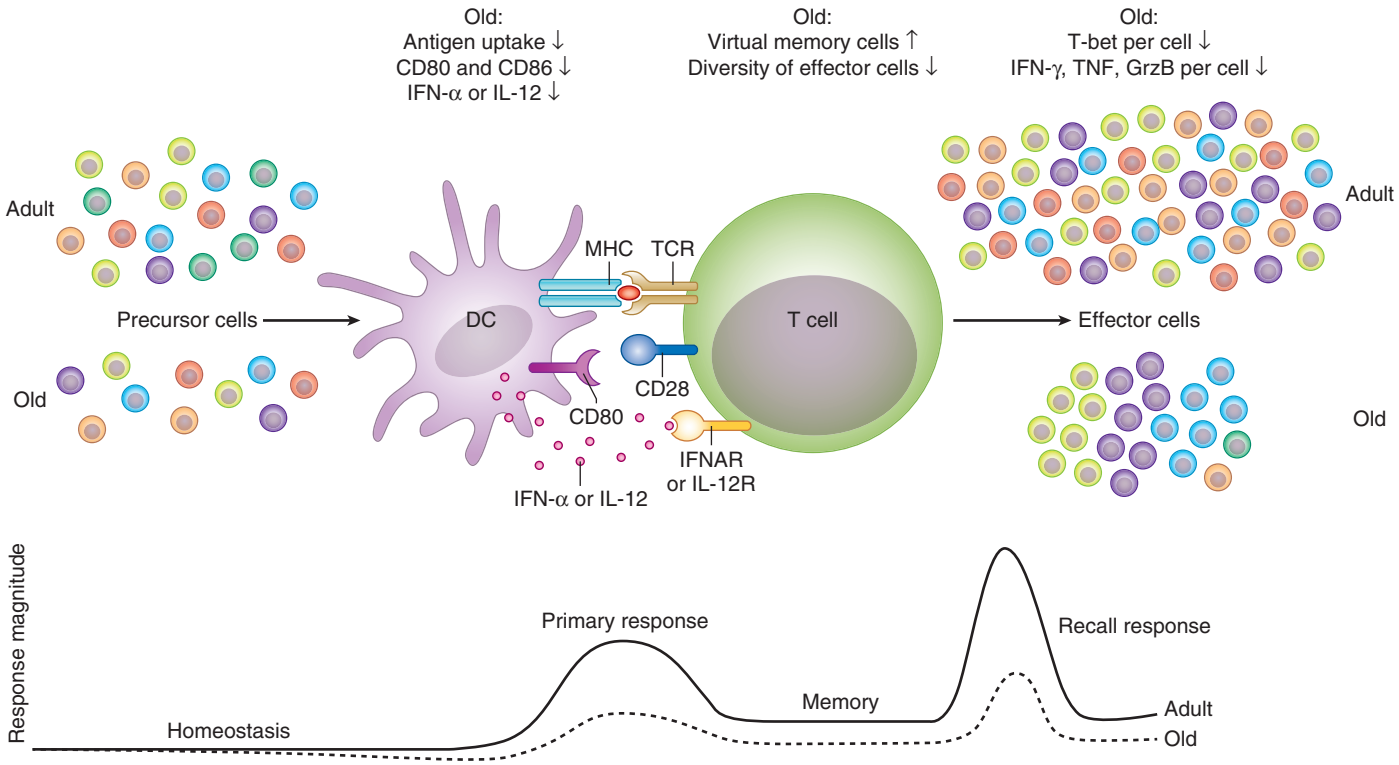


FIG. 310.2 Adaptive immune changes with aging lead to reduced primary and secondary responses, lower numbers of naïve cells and expanded memory cell compartments, and reduce diversity of effector cells. *CD80,* Cluster of differentiation 80; *GrzB,* granzyme B; *IFN-α,* interferon-α; *IFNAR,* interferon-α receptor; *IL-12,* interleukin-12; *IL-12R,* interleukin-12 receptor; *MHC,* major histocompatibility complex; *TCR,* T-cell antigen receptor. *(Reprinted with permission from Nikolich-Žugich J. The twilight of immunity: emerging concepts in aging of the immune system.* Nat Immunol. *2018;19:10–19.)*

have been powered to assess clinical outcomes. It is quite clear that age itself is associated with reduced responses to vaccines as early as the third or fourth decade (human papilloma virus, hepatitis B), but the deficit grows throughout adulthood such that efficacy of influenza and pneumococcal vaccines is questionable by the eighth and ninth decades. Specific vaccine formulations, very different from those used to boost early childhood responses, have been developed to try to overcome immune senescence; these include greater antigen concentration (e.g., high-dose influenza vaccine)[3] or a mixed-action adjuvants (e.g., zoster subunit vaccine)[4] and appear to substantially mitigate immune senescence, not only enhancing postvaccine markers of immunity but reducing clinical disease risk.

Nutrition

Protein-energy malnutrition (PEM) is common in older adults; 30% to 60% of subjects ≥65 years of age admitted to the hospital have PEM,

which is linked to delayed wound healing, pressure ulcer formation, risk of CAP and nosocomial infection, longer hospital stays, and increased mortality. PEM often goes unrecognized outside the hospital, but even mild PEM (i.e., seniors with a serum albumin of 3.0–3.5 g/dL) demonstrate reduced vaccine responses. Despite this, the role of high-protein/high-calorie nutritional supplements for preventing infection or boosting immune responses remains controversial and largely an open question except for those with specific indications (e.g., wound healing).

Specific micronutrient deficiencies in older adults have also been linked to poor immune function (e.g., vitamin B_{12} deficiency and inadequate pneumococcal vaccine responses) and risk of infection (e.g., vitamin D deficiency linked to risk of tuberculosis [TB] and *Clostridioides difficile* [formerly *Clostridium difficile*] infection). Nutritional supplements have been studied as a means to reduce infection risk and boost immunity in older adults, and all experts agree that if true deficiency exists it should be corrected. However, in otherwise healthy adults with normal or "insufficient" (but not deficient) vitamin levels the answer is less clear. Although some data support the use of multivitamins, zinc, selenium, vitamin E (in low-modest doses), and vitamin D, inconsistent results have been achieved.[5] More work is required to define the role of vitamin or mineral supplementation for augmenting immune response in this population.

Social and Environmental Factors

Additional "social determinants of health" combine to influence infection risk in seniors. Population-based studies reveal that lower income is associated with higher rates of CAP and invasive pneumococcal infections among older adults. Lower socioeconomic status (SES) may predispose to infection due reduced access to care, which is well documented in seniors, but low SES is also associated with increased exposure to infectious agents (e.g., grandparents raising young children more often), poor nutrition, and increased risk of comorbid disease (e.g., asthma and exacerbations due to pollution/tobacco exposure).

Environment plays a distinct role in long-term care (i.e., nursing home) residents, who have a particularly high incidence of respiratory, genitourinary (GU), gastrointestinal (GI), and skin infections, and unique infection control challenges exist in the long-term care setting.[6] Close contact between residents and staff plays a key role in the spread of respiratory infections (e.g., influenza, respiratory syncytial virus [RSV]), or infections transmitted by contact (e.g., *Streptococcus pyogenes, C. difficile*). Many frail older adults in a confined setting can lead to severe outbreaks with high mortality rates; proximity of residents, poor adherence to basic infection control measures, and the intense use of antibiotics also increase the risk of antibiotic-resistant bacteria in this setting.

PRESENTATION OF INFECTION IN SENIORS

Infection, even serious life-threatening infection, frequently presents with atypical features in older adults.[7] Serious infections may be signaled by seemingly trivial, nonspecific declines in function or mentation and underlying illness (e.g., congestive heart failure or diabetes mellitus) may be exacerbated by infection, leading older adult patients to seek medical attention for symptoms related to comorbidity rather than infection. The most fundamental sign of infection, fever, is absent in up to one-third of older adults with serious infection. Several studies show that frail older adults have lower mean baseline body temperatures than the currently accepted normal of 98.6°F (37°C). Further, temperature increases in response to pyrogens are diminished with advanced age. The decline in basal temperature and blunted response to pyrogens make it more likely that an older adult will have a body temperature within the "normal" range despite infection, and a normal temperature with significant infection often leads to delayed diagnosis and treatment.

Cognitive impairment may also contribute to the difficulty of diagnosing infection in older adults, with patients unable to communicate symptoms. This can lead to overdiagnosis, as well when colonization (e.g., asymptomatic bacteriuria) is often assumed to be the cause of nonspecific symptoms. Clinicians often have a lower threshold to pursue objective assessments (e.g., laboratory and radiologic evaluations) for infection in cognitively impaired older adults, given the difficulty interpreting subtle function changes and the absence of classic signs of infection noted above. Although a high index of suspicion is warranted, clinicians should be cautioned not to overevaluate and to interpret results carefully. The poor usefulness of culture data in some situations (e.g., swab cultures of skin surface wounds or urine cultures when catheters are present) in which positive cultures are a certainty can lead to overdiagnosis and over treatment (see later).

Changes in anatomy and physiology due to age and/or comorbidity may confound interpretation of diagnostic evaluations as well. For example, there is diminished sensitivity of transthoracic echocardiography (TTE) for detecting valvular vegetations in endocarditis in older adults due to calcification and other anatomic changes associated with age (summarized in reference 8). Studies suggest the sensitivity of TTE is 85% to 90% in adults age ≤55 years but is reduced to <50% for those older than 70 years. More frequent use of transesophageal echocardiogram (TEE) is therefore needed in seniors, where sensitivity returns to 85% to 90% and specificity is not reduced.

ANTIBIOTIC MANAGEMENT IN SENIORS

Antimicrobial Treatment

Age and comorbidity change drug distribution, metabolism, excretion, and interactions.[9] Antibiotic dose reductions are occasionally required in the older adults due to reduced renal function or predisposition to specific side effects, but the most prevalent complications include drug interactions, which are more frequent because older adults more commonly take multiple medications. Digoxin, warfarin, oral hypoglycemic agents, theophylline, antacids, and H2-receptor antagonists are commonly administered and have significant interactions with commonly prescribed antibiotics.

The changes in physiology with age often lead clinicians to the dictum of "start low, go slow" when administering new medications in older adults. However, for antibiotics this is *not* an appropriate strategy. Data suggest higher antibiotic levels are particularly important for efficacy in older adults—much more important than in young adults who often have more robust immune responses and greater physiologic reserve. In older adults, outcomes of serious infection are more dependent on reaching adequate drug levels earlier than in young adults. This is especially true for antibiotics with a concentration-dependent mechanism of action (e.g., fluoroquinolones). Further, slowed gastric motility, decreased absorption, increased adipose tissue, and coadministration of other drugs can decrease blood levels of antimicrobials in older adults, and of course antibiotics reach tissues via blood flow, so poor perfusion to the site of infection, particularly in skin and soft tissue infections of the lower extremities, may reduce efficacy. Adherence may be limited by poor cognitive function, inadequate understanding of the drug regimen, impaired hearing or vision, and polypharmacy, and studies suggest that any regimen requiring greater than twice-daily dosing is associated with very poor adherence rates.

Outpatient parenteral antibiotic therapy (OPAT) is commonly used for syndromes that occur more frequently in older adults (e.g., endocarditis or osteomyelitis) but has been underused in older adults, often due to a lack of Medicare coverage in the past, and older adults were often admitted to nursing homes just to obtain appropriate therapy. With the institution of Medicare Part D, OPAT is now covered, although navigating the system to obtain reimbursement for both the antibiotic and the necessary supplies for administration takes considerable skill. OPAT has been shown to be safe and effective therapy in seniors that have adequate support and monitoring.

Antibiotic Stewardship

Seniors represent an important population in whom antibiotic stewardship can be very effective. Older adults, particularly nursing home residents, have some of the highest rates of multidrug-resistant organism colonization and infection. The presence of indwelling devices (e.g., urinary catheters, G-tubes) and those with marked functional impairment are at very high risk for acquiring and harboring multidrug-resistant organisms.[10] This is perhaps not surprising as those same residents are more likely to receive antibiotics. Of importance, however, antibiotic use in the nursing home is a factor that can be studied and altered as it is

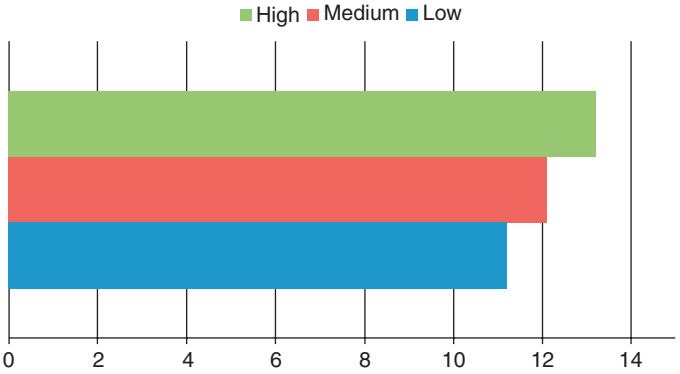


FIG. 310.3 Percentage of long-term care residents experiencing antibiotic-related adverse events with potential for indirect harm (*Clostridioides difficile* infection [CDI], non-CDI diarrhea/gastroenteritis, multidrug-resistant organism infection, allergic reaction, adverse drug reactions). Data are shown for nursing homes classified and high, medium, or low antibiotic use. *(Data from Daneman N, Bronskill SE, Gruneir A, et al. Variability in antibiotic use across nursing homes and the risk of antibiotic-related adverse outcomes for individual residents.* JAMA Intern Med. *2015;175:1331–1339.)*

more a characteristic of the nursing home than the individual patient.[11] Further, residents in nursing homes with high antibiotic use are more susceptible to adverse antibiotic-related events *even if the individual residents do not receive antibiotics;* just by being in a high-risk milieu they are more likely to suffer adverse consequences (*C. difficile* infection [CDI], non-CDI diarrhea, multidrug-resistant organism infection, allergic reaction, or general medication adverse events) (Fig. 310.3).

Setting minimum criteria for antibiotic administration in senior nursing home residents was proposed nearly 2 decades ago[12] but has yet to be implemented in most settings and thus its efficacy questioned.[13] Although comprehensive educational programs and in–nursing home consultation by infectious diseases specialists have been shown to reduce antibiotic use; systemic approaches are likely to be most effective. Culture stewardship refers to limiting the number of unnecessary cultures obtained (e.g., swab cultures of pressure ulcers, urine cultures in those with indwelling catheters) and can be particularly important for limiting antibiotic use in nursing home residents (Fig. 310.4A).[14] Cultures from such sites will *always* be positive, but the information does not correlate with clinically relevant cultures (e.g., bone biopsy under an ulcer or blood cultures in those with an indwelling urinary catheter and sepsis). Culture stewardship using preset criteria to obtain cultures can markedly reduce antibiotic use in this setting (Fig. 310.4B).[11]

Antibiotics at the End of Life

The 1998 American Medical Association Council of Ethical and Judicial Affairs included antibiotics, along with mechanical ventilation, as "life-sustaining" treatment that should be discussed as part of advanced directive and end-of-life care. Others argue that antibiotics are part of ordinary care, even for those who are designated to be receiving "comfort measures only." Although every clinical situation is unique, and no universal recommendation can be made for the using or withholding antibiotics in the terminally ill, it seems prudent to include antibiotic administration in the discussion of advanced directives as a potentially life-sustaining maneuver and to treat it no differently than any other medical intervention, such as surgery, mechanical ventilation, or administration of food/fluids. In those instances where palliation of symptoms is the major outcome desired (vs. prolongation of life), antibiotics should be administered only when symptoms are due to infection itself and readily reversible. Otherwise, restraint from even pursuing diagnostic testing for infection should be used.[15]

AGE-RELATED DIFFERENCES IN SPECIFIC CLINICAL SYNDROMES

A complete review of all the clinical infectious syndromes experienced by older adults is beyond the scope of this chapter, and many chapters in this textbook discuss aspects of individual conditions in seniors. However, some age- and/or function-specific aspects of prevalent syndromes deserve additional comment and appear later.

Pneumonia

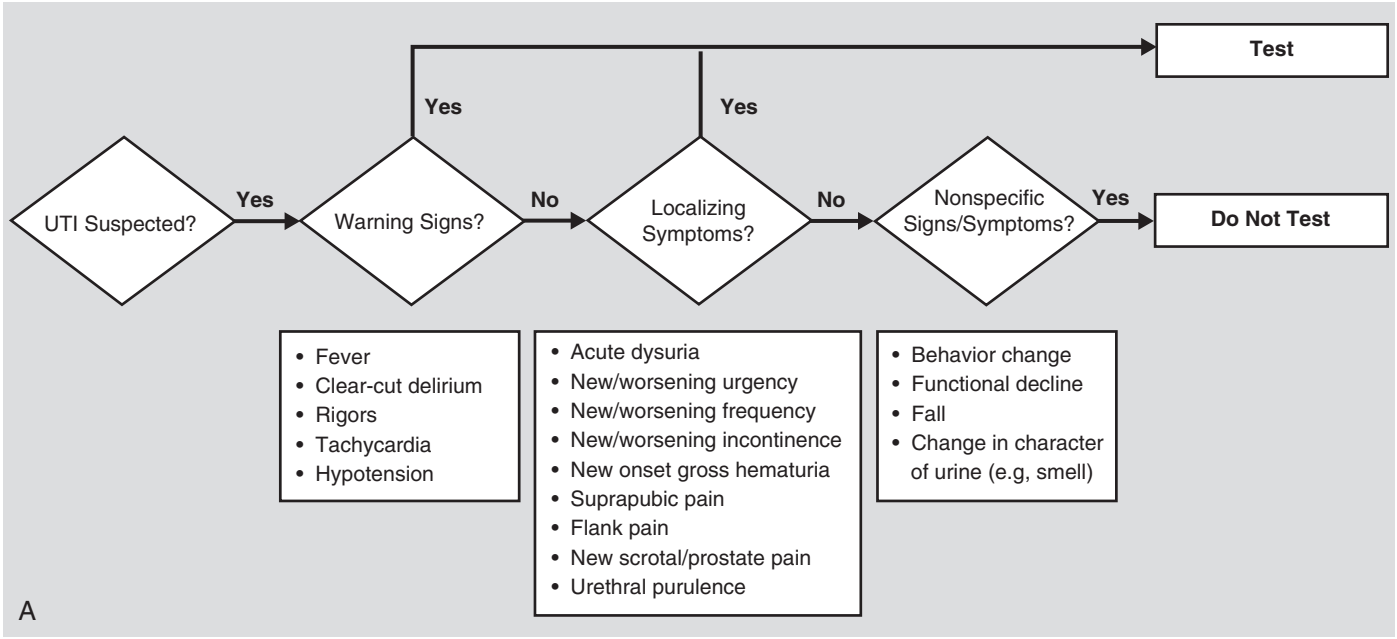
Older adults have a markedly increased risk of pneumonia versus young adults.[16] Comorbid cardiovascular and lung disease enhance risk, but age-related changes in physiology also contribute. Impaired mucociliary clearance with delayed clearance of secretions by the mucociliary mechanisms correlate with pneumonia risk. Further, chest wall mobility and compliance decline with advancing age due to loss of mobility and muscle strength, as well as changes in the rib cage when kyphosis or scoliosis is present. Lung compliance is reduced owing to impaired elastic recoil, which results in air trapping, higher residual volumes, and increased work of breathing. Finally, neurologic changes with age lead to "silent aspiration" secondary to reduced ability to cough, lower gag reflex, and frequent coexisting mental status changes or dementia.

The most common microbiologic causes of pneumonia in seniors are greatly impacted by place of residence. Seniors who dwell in long-term care facilities are more likely to have *Staphylococcus aureus*, gram-negative bacilli, and multidrug-resistant organisms isolated from clinical specimens than noted in specimens from community-dwelling seniors. Viral infection causing lower respiratory disease severe enough to require hospitalization is more common in seniors, especially those in long-term care, than in young adults and emphasizes the need to include viral diagnostics for older adults with pneumonia.[17] Outbreaks of influenza or RSV have been well documented in long-term care and need to be met quickly with prompt infection control measures and, when possible, chemoprophylaxis and vaccination strategies to limit spread.

Antimicrobial therapy recommendations for seniors are similar to those of all adults with pneumonia, with modifications based on risk factors for resistant organisms and severity of illness. Adjunct therapy with corticosteroids in those with severe community-acquired disease and a vigorous inflammatory response (usually defined as C-reactive protein >150 mg/L) has been recommended, as it appears to result in lower rates of respiratory failure and reduced length of intensive care unit (ICU) and hospital stay, although it has not been shown to reduce mortality.[18–20] Steroids are associated with higher rates of hyperglycemia, GI hemorrhage, and readmission after discharge. No individual studies or meta-analyses have focused on seniors, so no definite recommendations can be made. Older adults are more likely to suffer the complications of pneumonia mitigated by steroids and the adverse events associated with their use. In similar circumstances where older age is associated with higher risk, but also greater benefit (e.g., anticoagulation in atrial fibrillation), data suggest the concern for possible higher risk should not dissuade clinicians from using therapies where proven benefit has been shown. Thus this author suggests age alone not be a limiting factor when considering steroid use in pneumonia.

Urinary Tract Infection

Asymptomatic bacteriuria (ASB) is defined as the presence of bacteria in the urine, *with or without pyuria*, in the absence of clinical symptoms indicating a urinary tract infection (UTI). ASB is common in seniors, with rates of community-dwelling older adults (women > men) of up to 50% and even higher in long-term care residents. Much has been written about the prevalence of ASB in seniors, the importance of differentiating asymptomatic bacteriuria from true UTI, and the difficulties in making the diagnosis of UTI in seniors with subtle symptoms.[21] It is well beyond the scope of this chapter to fully review this literature, but comments on a few key concepts are warranted. First, testing for UTI in older adults should occur *only* when suggestive clinical symptoms (new fever, new/worse incontinence, dysuria, flank pain, delirium) are present because laboratory tests alone cannot differentiate ASB from UTI. (See earlier comments on "culture stewardship" and reducing unnecessary diagnostic tests of urine) (see Fig. 310.4). Second, the role of laboratory testing for UTI is primarily to *exclude* the diagnosis of UTI; with VERY rare exception, treatment for UTI should not be given to any older adult with a negative urinalysis or urine culture. Third, active monitoring and oral hydration even when testing shows bacteriuria and/or pyuria may successfully be used to manage seniors *without*



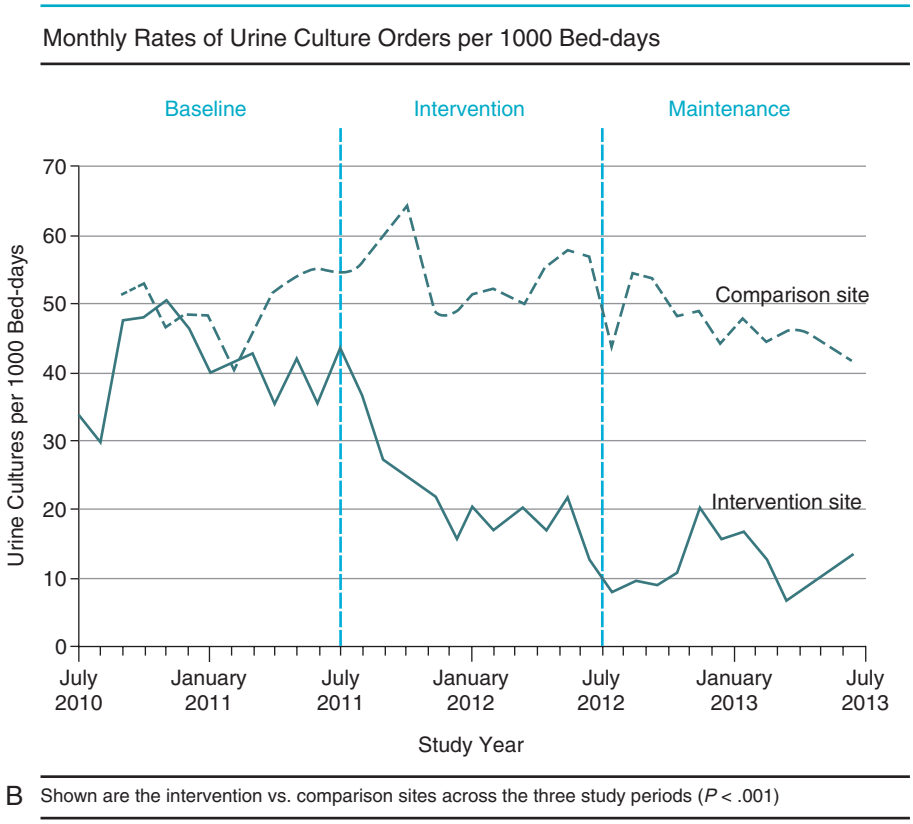


FIG. 310.4 (A) Example of decision-making process invoking "culture stewardship" for older adults with suspected urinary tract infection. (B) Impact of criterion-driven culture orders on the number of urine cultures obtained for hospital inpatients and nursing home patients. *(A reprinted with permission from McElligott M, Welham G, Pop-Vicas A, Taylor L, Crnich CJ. Antibiotic stewardship in nursing facilities.* Infect Dis Clin North Am. *2017;31:619–638; B reprinted with permission from Daneman N, Bronskill SE, Gruneir A, et al. Variability in antibiotic use across nursing homes and the risk of antibiotic-related adverse outcomes for individual residents.* JAMA Intern Med. *2015;175:1331–1339.)*

antibiotic use in those who do not have obvious urinary tract symptoms in situations that often prompt testing (e.g., mild temperature elevations of 99°–100°F, minor confusion/mental status change, "strong–smelling" urine).

Bacteremia and Sepsis

Early (within 1 month) mortality of sepsis for those older than 65 years is nearly 50% higher than that of younger adults, likely due to poor physiologic reserve, particularly in seniors with multiple comorbidities. Bacteremia rates are higher in older than in younger adults and more commonly arise from a GI or GU source. Therefore the causative agent is more likely to be a gram-negative bacillus, and antibiotic management of bacteremia and sepsis in older adults should emphasize the importance of initially broad coverage. This is particularly true when multidrug-resistant organisms risk is high (e.g., long-term care home resident, indwelling devices present).[22]

When older adults survive an episode of sepsis, they are more likely than young adults to suffer negative outcomes that reduce quality of life (e.g., impaired physical or cognitive function). In one study of seniors (average age, 78 years) surviving sepsis, moderate-to-severe cognitive impairment increased from about 6% before sepsis hospitalization to nearly 17% after hospitalization, and severe sepsis was associated with a threefold higher rate of moderate-to-severe cognitive impairment. These patients also had a decrease in activities of daily living (ADLs) and instrumental ADLs (IADLs).[23,24] Further, about 40% of those age 65 years and older require nursing home admission after surviving sepsis versus ≈15% of those younger than 65 years.[25]

Infective Endocarditis

Infective endocarditis (IE) is primarily a disease of older adults, except when IE is due to intravenous drug use, and occurs principally in those with degenerative valvular disorders and prosthetic valves (i.e., prosthetic valve endocarditis). In addition, indwelling devices, such as pacemakers and implanted defibrillators, are more frequently placed in seniors. IE in older adults presents a diagnostic challenge; fever and leukocytosis are less common (55% and 25%, respectively, in those 65 years and older versus 80% and 60%, respectively, for younger adults). Transthoracic echocardiography (TTE) has reduced sensitivity in older adults due to calcified valves, more turbulent blood flow, and shadows off prosthetic materials. TEE is more sensitive, and improves the diagnostic yield by 45% over that of TTE.

Native valve IE in young adults is typically caused by streptococci, staphylococci, and occasionally by HACEK organisms (*Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella, Kingella*). The same organisms predominate in older adults, but as noted for bacteremia earlier, GI and GU organisms such as enterococci and gram-negative rods become more common in seniors with IE. In consequence, initial antibiotic treatment is similar in young versus older adults; however, organism-specific therapy might vary based on age. Combination regimens with aminoglycosides are particularly problematic in the older patients because of toxicity (both renal and ototoxicity) but is occasionally unavoidable in certain circumstances (e.g., enterococcal IE). IE prophylaxis recommendations do not differ based on age alone.

Prosthetic Device Infections

Implantable prosthetic devices (prosthetic joints, cardiac pacemakers/heart valves, intraocular lens implants, vascular grafts, penile prostheses, etc.) are most frequently placed in older adults, and therefore infection of these devices is more common in this group.[26] Foreign material provides the milieu for bacterial biofilms and adherent bacteria are often more difficult for antibiotics or the immune system to kill. Causative organisms for early prosthetic device infections (<60 days after implantation) are frequently skin or nosocomial flora and reflect events around the time of implantation and/or the hospital stay associated with implantation. Coagulase-negative staphylococci predominate; *S. aureus* and diphtheroids are common as well. Gram-negative bacilli, fungi, or polymicrobial infection are rare causes of early infection. The pathogenesis of late infections is more likely due to occult bacteremia seeding the implant; thus older adults have a broader microbial differential than young adults, with greater incidences of gram-negative organisms due to GI and GU sources of bacteremia as noted previously, but staphylococci still predominate.

Cure of prosthetic device infections may be difficult with the device in place (see Chapter 105). However, in some instances early antibiotic intervention combined with aggressive surgical débridement may result in cure without removing the device (Fig. 310.5).[27] If early, aggressive therapy is ineffective in controlling the infection, and cure is the goal, it is imperative that the device be removed. However, desired functional outcomes should influence the management plan. When ambulation is not likely regardless of cure or many other comorbidities limit function, it may be most reasonable to control the infection long term with antibiotic suppression rather than attempt cure (see Fig. 310.5A). In contrast, age alone should *not* be a reason to withhold curative therapy; physical/cognitive function at baseline and the likely outcome should drive this decision, not age. For lifesaving devices, such as mechanical valves or implantable defibrillators, removal of the device is again most effective at producing cure, but suppression may be a best option when other conditions modify the overall goals of therapy.

An area of intense and prolonged debate is the need, or lack thereof, for antimicrobial prophylaxis surrounding dental, GI, and GU procedures in those with prosthetic devices. Although generally recommended for prosthetic heart valves and frequently used for vascular grafts, particularly within the first 12 to 24 months after placement, there is no evidence of demonstrated benefit for prophylaxis in patients with prosthetic joints, intraocular lens implants, intracoronary artery stents, cerebrospinal fluid shunts, breast implants, or other less commonly used prostheses. The American Dental Association recommends "considering" antibiotic prophylaxis for patients with prosthetic joint at "high risk"—joints placed within 2 years, immunosuppressed patients (including those with diabetes mellitus, rheumatoid arthritis, or malnourishment), or those with a previous joint infection (see Chapter 105).

Gastrointestinal Infections

Serious GI infections are more common in old than young adults. Altered transit time, achlorhydria, diverticular disease, immune senescence, altered GI microbiota, and comorbid diseases predispose seniors to GI infection. Most of these illnesses are diagnosed and managed similarly regardless of age; however, a number of aspects deserve further comment.

C. difficile disproportionately affects older adults, and this group also bears more morbidity and mortality due to CDI.[28] Many CDIs are acquired and/or expressed during acute hospitalization or long-term care residence. Asymptomatic carriage of *C. difficile* is not rare in seniors: 2% of elderly subjects in the community, 10% in community-dwelling seniors with outpatient health care exposure, and 20% to 50% in hospital or long-term care settings.[29] Symptomatic CDI occurs in about one in every seven carriers. Older adults with CDI are more likely to develop severe infection (sepsis, hypotension, renal failure, toxic megacolon), but even milder CDI can have major consequences more often in those with advanced age. In young healthy adults, using the bathroom 6 to 8 times daily may be aggravating. In an older adult with decreased mobility, visual impairment, or dementia, having to urgently defecate 6 to 8 times daily may lead to loss of independence and institutionalization.

Guideline-driven therapy should be used for CDI and varies by severity of infection, primary versus relapsed infection, and other considerations (e.g., cost, drug interactions).[30] In recent years, fecal microbiota transplantation (FMT) has become standard for patients experiencing multiple relapses and can be done using oral capsules of freeze dried material, with success rates reported in the literature of 80% to 90%.[31] As opposed to most randomized trials of new therapies, the majority of subjects in FMT trials are older adults, and FMT has been shown to be safe and effective. Similarly, older adults predominated in trials demonstrating that passive antibody administration reduces the risk of CDI in those with prior CDI and about to receive antibiotics.[32] This approach is now in trials for primary CDI prevention.

Tuberculosis

Advanced age has long been established as a major risk factor for developing TB. Several studies have demonstrated that, when compared with young adults, older adults are less likely to present with fever, night sweats, cough, or hemoptysis, and more likely to present with nonspecific symptoms of dizziness, nonspecific pain or mental "dullness," a prior history of TB, and a concomitant diagnosis of underlying cancer (summarized in[33]). Older adults are more likely to have widespread lung infiltrates, whereas young adults are more likely to have isolated upper lobe infiltrates/cavities, and older adults are more likely to have evidence of malnutrition (i.e., reduced serum albumin).

Probably the most important issue of TB management in older adults remains the challenge of diagnostic testing. The sensitivity of the tuberculin skin test (TST) to detect latent infection declines with age, with immune senescence likely playing a role. New diagnostic tests for TB (i.e., interferon-γ release assay [IFGRA] from blood, measured after ex vivo *Mycobacterium tuberculosis* antigen exposure) unfortunately only modestly improve sensitivity. The pooled sensitivity from multiple studies appears to be ≈70% for TST versus ≈75% for IFGRAs. The specificity of IFGRA is better than TST in those who have received bacillus Calmette-Guérin immunization.

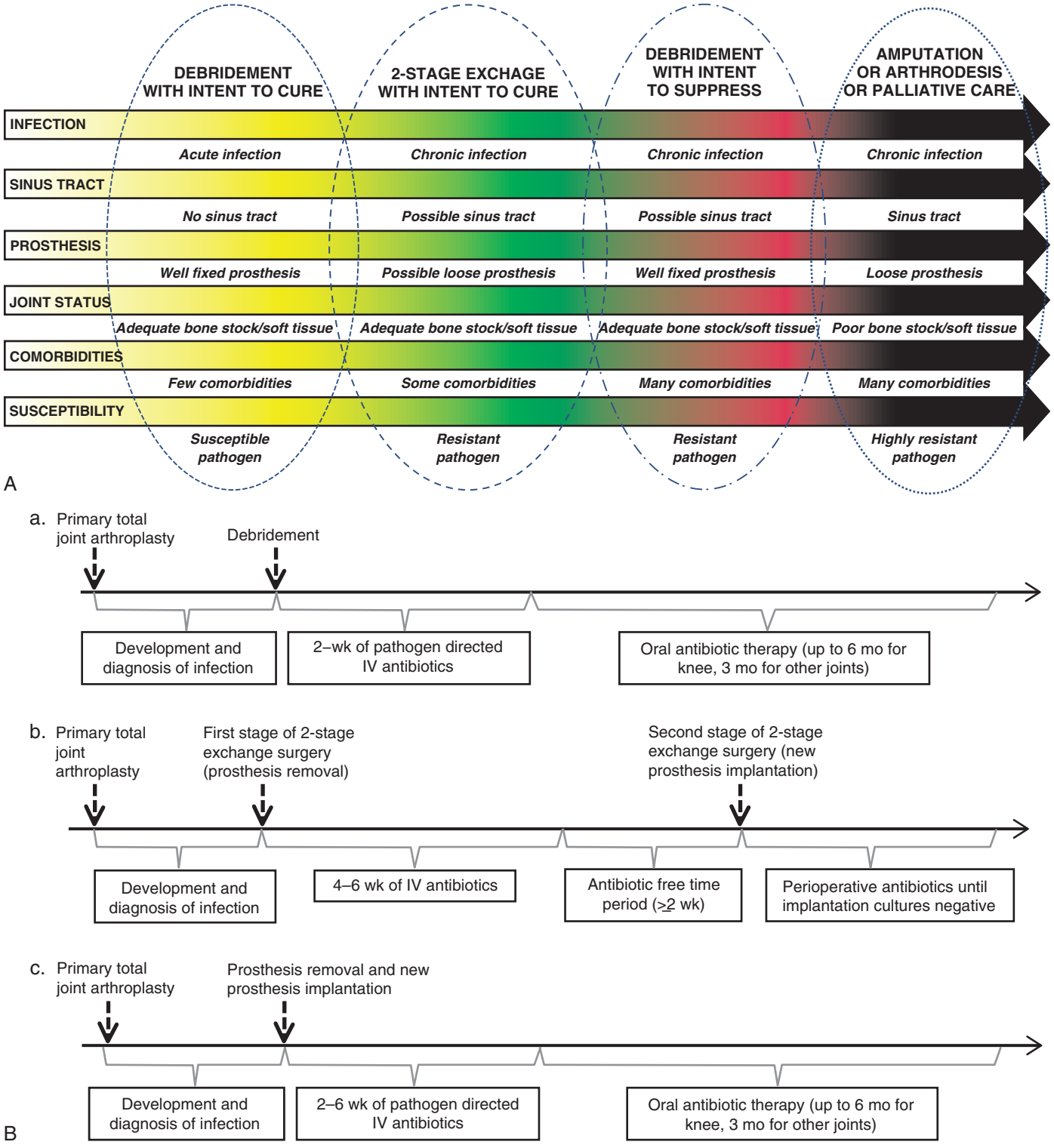


FIG. 310.5 (A) Factors that influence the treatment strategy of prosthetic joint infection in seniors. (B) Guideline recommended management in prosthetic joint infection when débridement-retention (a), two-stage (b), or one-stage (c) surgical intervention is used. *IV,* Intravenous. *(A and B reprinted with permission from Nair R, Schweizer ML, Singh N. Septic arthritis and prosthetic joint infections in older adults.* Infect Dis Clin North Am. *2017;31:715–729.)*

The treatment of TB in older adults does not differ from that of young adults, but older adults are more susceptible to adverse effects and drug-drug interactions.

Human Immunodeficiency Virus

Antiretroviral therapy (ART) advances have transformed human immunodeficiency virus (HIV) infection into a chronic illness—in other words, one "ages" with HIV and its treatment over a lifetime.[34,35] In fact, the majority of persons living with HIV (PLWH) in the United States are now older than 50 years due to effective treatment. The remarkable gains in HIV treatment have somewhat overshadowed the fact that, although PLWH can be expected to live into their 70s, their average life expectancy continues to lag the general population by about 5 years. Further, PLWH have a higher prevalence of age-related morbidities, including cardiovascular disease, hypertension, diabetes mellitus, bone fractures, cognitive impairment and dementia, cancer, and kidney

and liver disease; mechanisms of enhanced disease risk are slowly being unraveled.[36] Because of this they are more likely than HIV-uninfected persons to experience multimorbidity and even geriatric syndromes (frailty, falls, social isolation).

There is ongoing debate as to whether HIV accentuates age-related events (i.e., is a risk factor for multiple diseases, such as diabetes mellitus or smoking) or truly accelerates the hallmarks of the aging process itself (e.g., DNA methylation, telomere shortening, cellular senescence).[37] Complicating this area of research, there are dramatic cohort effects within PLWH, depending on prior ART exposure (e.g., prolong stavudine exposure with associated lipodystrophy, serial monotherapy before combination therapy, tenofovir-specific bone and kidney effects) that make it very difficult to separate the influence of HIV itself versus its treatment at a given time in history. It does appear, however, that the massive viral replication and associated die-off of immune cells during acute HIV infection is a cataclysmic biologic event of lasting consequence, much like a prolonged ICU stay, bout with cancer/chemotherapy, or other serious illness.[38,39] Aging mechanistic studies suggest this impact is equivalent to about 5 to 7 years of additional "biologic" aging that worsens the longer HIV goes uncontrolled and is not fully reversed by current therapies.

Fever of Unknown Origin

Fever of unknown origin (FUO) is classically defined as temperature >101°F (38.3°C) for at least 3 weeks and undiagnosed after 1 week of medical evaluation. FUO etiology varies by age and these differences should influence the diagnostic workup.[40] The cause of FUO can be determined in 90%-plus of cases, and approximately one-third will have treatable infections (e.g., intraabdominal abscess, bacterial endocarditis, TB, or occult osteomyelitis). In contrast to young adults, autoimmune disease is a more frequent cause of FUO in adults older than 60 years, accounting for about 25% of all FUOs in seniors. Systemic lupus erythematosus, the most common autoimmune cause of FUO in young adults, is absent in FUO series of older adults and is replaced by temporal arteritis (TA) and polyarteritis nodosa. Neoplastic disease accounts for another 20%, most often a result of hematopoietic malignancies (e.g., lymphoma and leukemia). Drug fever is a common cause of FUO in older adults, and deep venous thrombosis, with or without recurrent pulmonary emboli, occasionally causes FUO in older adults.

The approach to diagnosis in FUO for older adults should be influenced by the differential diagnosis. A thorough history and physical examination; basic laboratory evaluations of complete blood counts with differential, serum chemistries and hepatic enzymes, thyroid function studies, erythrocyte sedimentation rate (ESR), placement of a TST or performance of an IFGRA, a chest radiograph, and initial blood and urine cultures should begin the search. If the diagnosis continues to be obscure and the ESR is elevated, temporal artery biopsy, even in the absence of typical history or objective physical findings, should be strongly considered. If there is a low suspicion for TA, chest/abdominal/pelvic computed tomography is most likely to provide assistance.

IMMUNIZATION OF OLDER ADULTS

Immunization recommendations for older adults are constantly being updated. The latest consensus recommendations can be found at the Centers for Disease Control (CDC) web site at www.cdc.gov/nip/publications/ACIP-list.htm.

Pneumococcal Vaccine

Pneumococcal immunization is recommended for all seniors in this age group and for many patients younger than 65 years with comorbid conditions. Two vaccines are available: a 23-valent polysaccharide vaccine (PPSV23) and a 13-valent pneumococcal conjugate vaccine (PCV13). In 2014 recommendations from the Advisory Committee on Immunization Practices (ACIP) for pneumococcal vaccination in older adults were revised such that both PCV13 and PPSV23 should be given sequentially—PCV13 given first, followed by PPSV23 6 to 12 months later. For those already immunized with a first dose of PPSV23, repeat immunization is recommended with PCV13 as long as 1 year or more has passed since PPSV23 was administered. Another dose of PPSV23 should be given 6 to 12 months later and ≥5 years after the most recent dose of PPSV23; a minimum interval of 5 years between PPSV23 doses should be maintained. Studies of revaccination demonstrate that adverse events are uncommon and mild. Thus, when the pneumococcal immunization history is unknown, the vaccine should be administered.

Implementing current pneumococcal vaccine recommendations remains the greatest obstacle to prevention of fatal *Streptococcus pneumoniae* disease in the older adults. According to CDC estimates, only 40% to 50% of eligible older adults receive pneumococcal vaccine, and many unvaccinated older adults saw a medical practitioner or were even hospitalized within the prior 6 to 12 months. The CDC and its Advisory Committee on Immunization Practices (ACIP) have outlined several strategies for improving vaccine administration, including age-based, community-based, and provider-based strategies.

Influenza

The current ACIP recommendations are for all persons age 6 months and older be immunized each year. Medical personnel and caregivers for high-risk patients should be immunized to reduce transmission to those at increased risk for complications. There are multiple formulations of influenza vaccine (see Chapter 165 for details), but a high-dose influenza vaccine formulation is more effective than a standard-dose vaccine in older adults for preventing influenza-like illness (relative efficacy, 24.2%; 95% confidence interval [CI], 9.7 to 36.5) and serious events possibly related to influenza, reducing overall events by 17.7% (95% CI, 6.6% to 27.4%), serious pneumonia by 39.8% (95% CI, 19.3% to 55.1%), and all-cause hospitalizations by 6.9% (95% CI, 0.5% to 12.8%).[3]

Zoster

Zoster is much more common and more likely to cause long-term sequelae in older adults than in young adults. A live-virus zoster vaccine was approved in 2006 and reduces the risk of zoster by about 50% and the risk of clinically significant postherpetic neuralgia by about 60%. However, in 2015 data were published regarding a two-dose regimen of an adjuvanted subunit zoster vaccine that is much more efficacious, preventing zoster in ≈97% of recipients, even those age 70 years and older.[4] Based on these data the US Food and Drug Administration has now approved the vaccine, and ACIP now recommends administration of two doses of recombinant zoster vaccine (RZV; Shingrix) 2 to 6 months apart to adults age 50 years or older, regardless of past episode(s) of herpes zoster or prior receipt of zoster live-virus vaccine (Zostavax). The RZV does have a greater risk of local reaction, but the vast majority of cases are manageable with symptomatic treatment.

Other Vaccines

The older adult population is the group most at risk for tetanus in the United States, with women being particularly susceptible because of a lower likelihood of receiving boosters associated with minor/moderate trauma than in men. A complete tetanus vaccine series is indicated for persons with an uncertain history and for those who have received fewer than three doses. Boosters should be given at 10-year intervals, or more frequently with high-risk injuries.

Pertussis, although usually diagnosed in infants and young children, is often propagated by older adults with incomplete immune protection. Pertussis protection wanes with age, and all adults, including those 65 years and older, should receive an acellular pertussis formulation (TdaP) at least once as one of their scheduled tetanus boosters.

Hepatitis vaccines are also indicated for some older adults. Hepatitis B vaccine is indicated for older adults at risk (e.g., renal failure), but seniors are also commonly volunteers at health care facilities and should be considered at risk if they engage in any patient contact. Hepatitis A vaccine is indicated in more limited circumstances, such as chronic hepatitis C, travel, and for men who have sex with men. Unfortunately, the efficacy of hepatitis A and B vaccines in older adults is unknown but may be much lower than in young adults. Age-related declines in response to the vaccine, with antibody titers below those considered protective that can be noted as early as age 35 years; by age 70 years

less than half of adults given hepatitis B vaccine and only two-thirds of those given hepatitis A vaccine will produce antibody levels considered protective. Early results indicate that immunogenicity in the elderly may be improved with the recently marketed recombinant hepatitis B vaccine with a novel adjuvant (Heplisav-B).[40a]

TRAVEL RECOMMENDATIONS FOR OLDER ADULTS

Older adults are among the most widely traveled members of society, including to countries that require cholera and yellow fever vaccines. However, the yellow fever vaccine is a live-virus vaccine, and data suggest that older adults are six times more likely than young adults to experience a serious adverse event. Furthermore, although still quite rare, reactions requiring hospitalization or resulting in death occur more frequently in seniors than in young adults.[41] Because the incidence of yellow fever in travelers is very low, particularly when travel is limited to urban areas, a compelling case to administer the vaccine should be required before administering yellow fever vaccine in older adults. Often the reason given is that countries may deny access to those who cannot prove recent immunization, but a physician's letter of exemption is often acceptable.

Malaria chemoprophylaxis can be difficult in the older adults. Side effects are more common for many agents (e.g., mefloquine may produce dizziness, change in mental status, and bradycardia or prolonged QT intervals), and coadministration may be difficult in those taking cardiac medications or with significant heart disease. Alternative regimens are available, but recognition of current resistance patterns is critical (see CDC website [www.cdc.gov/travel] for up-to-date information).

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311 Infections in Asplenic Patients

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SHORT VIEW SUMMARY

Epidemiology
- Infection occurs in patients with congenital asplenia (rare), acquired asplenia secondary to splenectomy or sickle cell anemia, and acquired hyposplenia secondary to inflammatory or autoimmune disorders or human immunodeficiency virus–acquired immunodeficiency syndrome.
- The incidence is seven to eight severe infections per 100 person-years in postsplenectomy adults.
- Risk factors for infection include young or old age, occurrence less than 1 year after splenectomy, indication for splenectomy (immune cytopenias > trauma > incidental), lack of appropriate vaccines, and lack of prophylactic antibiotics in young children.

Microbiology
- Encapsulated bacteria (*Streptococcus pneumoniae, Haemophilus influenzae,* and *Neisseria meningitidis*) are the classic pathogens of postsplenectomy sepsis.
- With widespread use of vaccines against encapsulated bacteria, *Staphylococcus aureus* and gram-negative enteric bacteria are seen more commonly.
- Asplenic patients are at risk for increased severity of malaria, babesiosis, and anaplasmosis.

Diagnosis
- Blood culture is the most important test to identify postsplenectomy sepsis and must be obtained at the earliest sign of infection.
- White blood cell count may be elevated or depressed.
- Cerebrospinal fluid examination may be indicated in severe sepsis.
- Evidence of disseminated intravascular coagulation or vascular collapse may accompany sepsis.

Treatment
- Immediate empirical antibiotic therapy is key to preventing fulminant bacterial infection.
- Self-administered, oral antibiotics (amoxicillin-clavulanate, cefuroxime, or fluoroquinolone) may be used by asplenic patients at home at first sign of infection, followed by immediate visit to an emergency facility.
- Empirical systemic antibiotics (vancomycin + ceftriaxone or a fluoroquinolone) must be started immediately at an emergency facility (after blood culture but before other diagnostic tests).
- Definitive antibiotic therapy will depend on the identification and antibiotic susceptibility of the infecting pathogen.

Prevention
- Patient education, repeatedly reinforced, is the responsibility of all health care providers.
- Avoid splenectomy if possible.
- Administer appropriate vaccines (Hib, PCV13, PPSV23, MCV4, MenACYW, MenB, influenza), as recommended by the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention.
- Prophylactic antibiotics are recommended for children younger than 5 years, those who are immunocompromised, or patients with past history of sepsis.
- Avoid vectors that carry the parasites causing malaria, babesiosis, and anaplasmosis.

After discovery of the spleen, which occurred sometime during the dawn of human dissection, its true role in health and disease remained a mystery for many generations. At the time of Galen, the spleen was thought to be important in removing "black choler" from the body; black choler (or black bile), according to Hippocrates, was one of the four humors thought to regulate bodily functions. The spleen and its various secretions were also implicated in a number of emotional imbalances. Excess black choler due to splenic failure was thought to be the cause of melancholy, whose name is derived from the words for "black" and "bile." Further, a person described as "splenetic" was hot-tempered or hasty in judgment, and "venting one's spleen" suggests a burst of pent-up anger. Black choler, a cold humor, was believed to counteract the effects of the two hot humors (blood and phlegm). Although the fourth humor, yellow bile, was known to be excreted by the gallbladder into the intestine, the mode of excretion of black bile was not known to the ancients.[1]

More recently the spleen has been recognized for its important role in protecting vertebrates from infection. It represents approximately 25% of the total lymphoid mass of the human body and contains half the body's monocytes and immunoglobulin-producing B lymphocytes.[2] Although not vital to human survival, the spleen plays an important role in the host's ability to combat both invasive bacteria, particularly those possessing polysaccharide capsules, and intraerythrocytic parasites.

ANATOMY OF THE SPLEEN

The embryonic precursor of the spleen is the mesenchyme of the dorsal mesogastrium, and the splenic red and white pulp are developed by the sixth month of fetal life. Normally located posteriorly in the left side of the peritoneal cavity, the spleen sits below the diaphragm, and its hilum, which contains the splenic artery and vein, is in close proximity to the tail of the pancreas. The normal organ is roughly the size of the patient's fist and weighs between 80 and 200 g in adult males and 70 and 180 g in adult females, but it can quickly enlarge in response to infection or inflammation. Aerated blood enters the spleen from the aorta via the splenic artery and short gastric arteries and, like the thymus, the spleen possesses only efferent lymphatic vessels. The normal spleen, which receives approximately 6% of the cardiac output,[3,4] is surrounded by a fibromuscular capsule.

The spleen consists of three anatomically distinct zones: red pulp, white pulp (seen as white nodules on the cut surface), and marginal zone (Fig. 311.1). Red pulp, the largest component of the spleen, is composed of a complex network of endothelium-lined venous sinuses and the Billroth cords, which contain fibrils, connective tissue, and large numbers of macrophages. White pulp, made up of islands within the red pulp that are composed of reticular structures that surround penicilliary arterioles, contains primarily T lymphocytes within the periarteriolar lymphoid sheath, as well as fewer B lymphocytes and natural-killer lymphocytes. Lymphoid follicles arise within this sheath, and on immunologic stimulation, the activated follicles form germinal centers similar to those seen in reactive lymph nodes. Located at the intersection of the red pulp and white pulp, the marginal zones are composed primarily of B cells (including memory cells) but also contain both T cells and antigen-presenting cells, such as Toll-like receptor–bearing macrophages or dendritic cells. Thus white pulp and the marginal