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# Sepsis and other Infectious Disease Emergencies in the Elderly

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## Introduction

The world is aging. The number of individuals aged 60 years and over is expected to increase globally from 841 million in 2013 to more than 2 billion by 2050.[1] In the United States, persons aged 65 years and over are anticipated to double in number from 43.1 million in 2012 to 83.7 million by 2050.[2] Fueled by a generation of baby boomers born between 1946 and 1964, more than a fifth of the U.S. population will surpass the age of 65 years by 2030. From 2009 to 2010, elders accounted for more than 19 million visits made to U.S. emergency department (ED) visits, representing 15% of all ED visits nationally.[3] More than a third of these visits warranted hospital admission for further care. As new advances in medicine and improved access to healthcare continue to extend the envelope of life expectancy worldwide, emergency physicians must be well-versed in the timely, comprehensive, and compassionate care of our elders.

Infectious diseases account for widespread morbidity and mortality among the elderly. In 2012 alone, infectious diseases accounted for 13.5% (3.1 million) of all visits made by elders to U.S. EDs.[4] Hospitalization rates for infectious diseases in this segment of our population have steadily risen over the past two decades.[5,6] While respiratory tract infections, primarily pneumonia, account for the majority of these admissions, hospitalization rates for sepsis and urinary tract infections have dramatically increased since 2000, particularly in those aged 85 years and over.[7] From 1998 to 2004, infectious diseases accounted for almost 14% of all hospitalizations of older adults in the U.S., with total charges in excess of $261 billion.[8] Not surprisingly, pneumonia and sepsis accounted for almost 60% of those charges. In a large retrospective study of 323 acute-care hospitals in

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California from 2009 to 2011, infection-related readmissions comprised more than a quarter of 30-day all-cause readmissions.[9] Although mortality from heart disease, malignancy, chronic pulmonary disease, and cerebrovascular disease far outpace mortality from infectious diseases in persons aged 65 years and over, pneumonia, influenza, and sepsis remain significant causes of death among elders in the U.S.[10]

The spectrum of infectious diseases in the elderly is wide-ranging. This review will examine the unique risk factors that render the elderly vulnerable to infection and focus on the diagnosis and emergent management of severe sepsis and septic shock, pneumonia, urinary tract infections, central nervous system infections, and skin and soft tissue infections.

## Aging and infection

The aging immune system creates a natural state of immunosuppression in the elderly, predisposing to infection. Immunosenescence is characterized prominently by a decline in adaptive immunity. While circulating memory T-cells increase over time in response to continued antigenic stimulation, the pool of naïve T-cells is depleted through age-related thymic involution, compromising the primary T-cell response to new antigens.[11,12] Loss of T-cell receptor repertoire diversity and intrinsic age-related naive T-cell defects further impair the effectiveness of this cell-mediated immune response. As the pool of antigen-experienced memory B-cells expands with age displacing naive B-cells necessary for new antibody formation, humoral immunity is likewise blunted. Reduced B-cell repertoire diversity, devolution of critical T-cell interactions needed for B-cell activation and differentiation, and decreased antibody affinity dampen the humoral response to infection and vaccines alike.[12] Immunosenescence is also marked by the dysregulation of innate immunity.[13,14] Polymorphonuclear neutrophils (PMN) exhibit reduced chemotaxis, phagocytosis, and intracellular killing of pathogens, due in part to reduced toll-like receptor (TLR) expression and activation. Similarly, age-associated decreases in macrophage, natural killer, and dendritic cell function are apparent. Impaired immune responses to new pathogens may also arise from basal activation of the innate immune system with increasing age, evidenced by increased levels of pro-inflammatory cytokines (*e.g.*, IL-6, TNF-α), clotting factors, and acute phase reactants (*e.g.*, C-reactive protein). Attributed to chronic viral infections (*e.g.*, cytomegalovirus) and cellular damage as well as age-related hormonal and metabolic changes, such dysregulated inflammatory responses may likewise contribute to the development of non-infectious diseases such as atherosclerosis and Alzheimer's disease.[14] The aging immune system is a complex phenomenon that we have yet to fully comprehend.

Physical barriers to infection such as the skin wane with age, hastened in the setting of immobility. Weakening of the gag and cough reflexes, incomplete urinary bladder emptying, and other age-related changes allow pathogens to access and establish infection in previously protected compartments. Surgical wounds and medical devices (*e.g.*, central venous catheters, urinary catheters, endotracheal tubes) commonly used in healthcare circumvent these natural defenses altogether. Prosthetic joints, heart valves, cardiac pacemaker-defibrillators, and other implanted hardware can serve as a nidus for infection. Dementia, impaired coordination, and frequent falls and injuries further predispose the elder

to infection. Malnutrition and peripheral vascular disease can impede wound healing. Other comorbid conditions, including diabetes mellitus, chronic obstructive pulmonary disease (COPD), chronic kidney disease, and malignancy, may also increase an elder's overall risk of infection. Those receiving immunosuppression for solid organ or bone marrow transplants, malignancy, or a host of inflammatory conditions are at even greater risk of infection involving a broad range of pathogens.

Atypical presentations are a hallmark of most diseases in the elder, often rendering the diagnosis of infection challenging. Non-specific symptoms associated with acute functional decline are common including confusion, frequent falls, difficulty ambulating, reduced food intake, dysphagia, incontinence, weight loss, and failure to thrive, all of which can also be seen in a wide range of non-infectious processes in the elderly. Age-related dementia and polypharmacy can further limit the clinician's ability to obtain a reliable history of symptoms from the patient. Underreporting or downplaying of symptoms by the patient can delay presentation to care for significant infections.

Fever, traditionally defined as a body temperature greater than 38°C (100.4°F), is absent or blunted in up to a third of elderly patients with an acute infection.[15] Diminished thermoregulatory capacity and abnormal production and response to endogenous pyrogens with aging may be partly to blame. In patients hospitalized with moderate-to-severe pneumonia, the average temperature during the first three days of illness decreases by 0.15°C (0.3°F) with each decade increase in age, equating to a 1°C (1.8°F) difference in temperature between a 20 year-old and 80 year-old patient with pneumonia.[16] Healthy elders are also likely to have lower baseline body temperatures than younger adults.[17] Febrile response may be delayed in many instances. In view of this, fever in older long-term care residents has been defined as: 1) a single oral temperature >37.8°C (>100.0°F); 2) repeated oral temperatures >37.2°C (>99.0°F) or rectal temperatures >37.5°C (>99.5°F); or 3) a >1.1°C (>2.0°F) increase in temperature above baseline, and it may be reasonable to apply this definition to the elderly population as a whole.[18] Tympanic thermometry is comparable in diagnostic accuracy to rectal thermometry for identifying infection when a lower fever cutoff of 37.3°C (99.1°F) is used; temporal artery thermometry is significantly less accurate.[19] However, body temperatures greater than 38°C (100.4°F) generally equate with serious illness in elders presenting to the ED.[20] Likewise, hypothermia relative to baseline body temperatures may also signal life-threatening infection, particularly in sepsis.[21]

## Severe sepsis and septic shock

Sepsis is a clinical syndrome that is characterized by a dysregulated inflammatory response to severe infection (Table 1). Severe sepsis is defined as sepsis-induced organ hypoperfusion and dysfunction, outwardly manifesting as acute kidney injury, coagulopathy, encephalopathy, acute respiratory distress syndrome (ARDS), and hypotension due to vasodilation, increased endothelial permeability, and functional adrenal insufficiency. Septic shock is distinguished by sepsis-induced hypotension that is refractory to adequate fluid resuscitation. More than half of all cases of sepsis in the U.S. occur in adults over the age of 65 years.[22,23] The relative risk (RR) for developing sepsis is 13.1 times greater in elders (95% confidence interval (CI), 12.6 to 13.6) compared to those under 65 years of age, and

elders are 1.56 times more likely to die from sepsis (95% CI, 1.52 to 1.61).[22] The incidence, disease severity, and mortality associated with sepsis is disproportionately high among the elderly, due in part to immunosenescence, prolonged host inflammatory responses, a tendency toward coagulation activation and impaired fibrinolysis, and an increased susceptibility to microbial mediators including endotoxin leading to profound and persistent hypotension.[24,25] This hyperinflammatory state is followed by profound immunosuppression as a result of T-cell exhaustion in elderly patients, further increasing mortality and morbidity through secondary infections.[26,27] While significant advances have been made in emergency and critical care, mortality can range anywhere from 12.1 to 25.6% in severe sepsis to 30 to 50% in septic shock.[28–30] Increasing age is an independent risk factor for severe sepsis and related mortality.[31] Nursing home residence, a likely marker of frailty and multiple comorbidities, has also been associated with an increased risk of severe sepsis and death in elders.[32]

Respiratory infections, bloodstream infections, and genitourinary infections are the most common underlying causes of sepsis in the elderly.[22,23,31,32] Elders are more likely to develop sepsis due to Gram-negative infections, particularly in the setting of pneumonia, and fungal infections compared to those <65 years of age.[22] Those residing in long-term care facilities or with frequent healthcare contact may be at risk for infection with multidrug-resistant organisms. Clinical presentations of sepsis in the elderly can be muted until overwhelming infection devolves into septic shock. Severe infections including those involving the bloodstream are heralded predominantly by atypical symptoms such as confusion, falls, malaise, incontinence, immobility, and syncope, rather than classic presentations of subjective fever, chills, cough, dysuria, or other symptoms of localized infection.[33–35] Elders with severe bloodstream infections are often febrile, but this may be less common with advanced age (>85 years).[34] Compared to younger adults, elders are less likely to be tachycardic and more prone to tachypnea and acute respiratory distress with severe infection.[34–36] Most elders mount a significant leukocytosis in the setting of sepsis and bloodstream infection.[34,35,37]

The initial management of severe sepsis and septic shock in the elderly patient should focus on timely empiric antimicrobial therapy and aggressive volume resuscitation in accordance with current established international guidelines.[38] While several paradigms have been proposed to explain the role of infection in triggering and sustaining the immunologic cascade leading to cellular injury, irreversible organ damage, and death in severe sepsis and septic shock, appropriate antimicrobial therapy is critical to rapidly reducing pathogen load and improving mortality.[39,40] Empiric antimicrobial therapy is considered appropriate if it has *in vitro* activity against a causative pathogen before it has been identified in the laboratory workup (*e.g.*, microbiologic culture, rapid molecular diagnostics). In a retrospective study of 5,715 patients with septic shock, inappropriate initial antimicrobial therapy occurred in almost 20% of patients and was associated with a five-fold reduction in survival.[28] For this reason, empiric antimicrobial therapy should cover both Gram-positive and Gram-negative bacteria. When available, hospital antibiograms can help inform empiric therapy by highlighting regional and patient population-specific differences in antimicrobial susceptibilities for common bacteria. The most likely anatomic source of infection should also guide antimicrobial selection so that therapeutic drug levels are achievable in infected

tissue and fluid (*e.g.*, lung, urine, cerebrospinal fluid). Recent hospitalization, residence in a long-term care facility, antimicrobial exposure, and prior colonization or infection with a resistant organism should prompt expansion of empiric therapy to include organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), and multidrug-resistant Gram-negative bacilli. Antifungal therapy is warranted in the setting of immunosuppression (*e.g.*, human immunodeficiency virus infection, hematologic malignancy, solid organ or hematologic stem cell transplant), neutropenia, prior extensive antimicrobial exposure, or extensive colonization with *Candida*. Empiric antimicrobial therapy should be initiated within the first hour of recognition of severe sepsis or septic shock. In a major retrospective study of septic shock, administration of appropriate antimicrobial therapy within the first hour of hypotension was associated with a 79.9% survival to hospital discharge.[41] Survival declined by 7.6% with each subsequent hour, with a survival rate of 42% at a median delay of 6 hours. Early and appropriate antimicrobial therapy is essential to survival in severe sepsis and septic shock.[42–44] Microbiologic cultures (*e.g.*, blood cultures) should be obtained prior to administering antimicrobials to help tailor pathogen-specific therapy but should not significantly delay treatment (>45 minutes), particularly in septic shock.

Pharmacokinetic and pharmacodynamic optimization of antimicrobial therapy to rapidly achieve therapeutic serum drug concentrations further enhances the clearance of pathogens in severe sepsis and septic shock.[39] Initial antimicrobial therapy should start at the maximum recommended dose while taking into account baseline renal or hepatic insufficiency that may predispose an elder to drug toxicity. Age-related changes in body composition, total body water, and serum albumin all impact drug concentrations. Interstitial third-spacing due to increased capillary permeability in sepsis can lead to sub-therapeutic drug concentrations for many antimicrobials. Clinical pharmacists can play an invaluable role in selecting dosing strategies that maximize antimicrobial effect in severe sepsis, septic shock, and other severe infections in the ED.[45] In addition to antimicrobial therapy, adequate source control (*e.g.*, abscess drainage, removal of an infected central venous catheter) is also integral to decreasing pathogen burden.

Protocolized, quantitative resuscitation strategies utilizing intravenous fluids, vasopressors, inotropes, and blood transfusions seek to correct the circulatory dysfunction that results from the intense inflammatory response in severe sepsis and septic shock. Early goal-directed therapy (EGDT) employing invasive hemodynamic monitoring has been shown to significantly reduce mortality in a landmark study.[46] However, several recent randomized, multicenter studies have failed to recreate the success of this strategy, likely due to improved awareness, timely diagnosis, and early treatment of severe sepsis and septic shock over the past decade.[47–49] Current guidelines support an initial minimum fluid challenge of 30 mL/kg of crystalloid in patients with sepsis-induced organ hypoperfusion, hypovolemia, or hyperlactatemia (≥4 mmol/L).[38] Additional fluid challenges may be administered based on dynamic or static measures of fluid responsiveness. Elders with congestive heart failure, chronic renal insufficiency, or end-stage renal disease may benefit from guarded resuscitation with smaller fluid boluses to avoid volume overload. Vasopressors are recommended in the setting of hypotension that has not responded to initial volume resuscitation, with norepinephrine being the preferred agent. While many sepsis intervention

trials include elderly patients, those with significant medical comorbidities at risk of death are often excluded.[50] Trials targeting high-risk elderly patients with severe sepsis or septic shock are greatly needed to better inform specific recommendations taking into account the altered physiology of aging. Nevertheless, standardized resuscitation protocols for severe sepsis and septic shock improve mortality in the elderly, likely through earlier recognition, empiric antimicrobial therapy, and aggressive volume resuscitation.[37]

Indicators of poor prognosis in elderly patients with severe sepsis include the presence of shock, elevated serum lactate levels, and organ failure (particularly respiratory or cardiac). When present, hypothermia is an independent predictor of increased mortality in elderly patients with sepsis.[21] Leukemoid reactions (white blood cell count $>30.0\times10^3/\mu L$) carry a grave prognosis in elderly patients with sepsis.[51] There is evidence to suggest that Predisposition Insult Response and Organ failure (PIRO), Sequential Organ Failure Assessment (SOFA), and Mortality in Emergency Department Sepsis (MEDS) scores may be useful in predicting mortality in elderly sepsis patients presenting to the ED.[52,53] Biomarkers including cardiac troponin I and N-terminal pro-brain natriuretic peptide (NT-proBNP) may also have a role in predicting mortality in elders with severe sepsis or septic shock.[54,55]

Elderly survivors of sepsis incur significant morbidity, frequently requiring skilled nursing and rehabilitative care after their acute hospitalization.[22] Severe sepsis exacts a considerable toll on elderly survivors in the form of long-term functional disability and moderate to severe cognitive impairment.[56,57] Controlling for individual pre-sepsis levels and trajectories of geriatric comorbid conditions (*e.g.*, cachexia, incontinence, injurious falls), higher rates of low body mass index ($<18.5\ kg/m^2$) have also been demonstrated in elderly survivors of severe sepsis, suggesting that severe sepsis increases sarcopenia, the age-related loss of skeletal muscle mass.[58] Such changes in brain function and body composition contribute to frailty, increasing an elder's need for assistance with activities of daily living and threatening their independence. Survivors of severe sepsis and other critical illness often require significant additional healthcare compared to their premorbid state, frequently in inpatient settings.[59] From the vantage point of both the patient and the healthcare system, the early recognition and treatment of infectious diseases commonly encountered in elderly patients presenting to the ED must therefore assume an added urgency in order to prevent progression to severe sepsis and septic shock. Likewise, candid discussions with patients, family, and other care providers in the ED centered upon patient preferences, goals of care, and anticipated clinical outcomes in severe sepsis and septic shock are particularly important given the high mortality and morbidity associated with this disease.

## Pneumonia and influenza

Sir William Osler penned, "pneumonia may well be called the friend of the aged."[60] Furthermore, "a knowledge that the onset of pneumonia is insidious and that the symptoms are ill-defined and latent, should put the practitioner on his guard."[60] A century later, this characterization of pneumonia in the elderly holds true. More than 900,000 cases of community-acquired pneumonia occur annually among U.S. seniors and approximately 1 in 20 adults over the age of 85 years develop CAP each year.[61] Pneumonia is the most common

infectious disease indication for hospitalization among adults over 65 years of age.[5,6] In 2013, influenza and pneumonia resulted in more than 48,000 deaths among elders in the U.S.[10] Elders are at increased risk for community-acquired pneumonia (CAP) due to impaired mucociliary clearance and diminished protective cough reflexes which allow inhaled or aspirated pathogens to gain access to the lower respiratory tract. Increased lung compliance and reduced vital capacity contribute to decreased functional reserve in old age, rendering the elder less able to compensate for serious pulmonary infection. This is compounded by chronic pulmonary disease (*e.g.*, COPD), asthma, and tobacco dependence, all well-established risk factors for CAP.[61] Congestive heart failure, diabetes mellitus, poor functional status, low body weight, and recent weight loss also place elders at risk for developing pneumonia.[61,62]

A combination of cough, fever, and dyspnea was absent in two thirds of elders diagnosed with CAP in one study, while almost half presented with delirium or acute confusion.[63] Fever was absent in more than a third of elders. Other symptoms including chills, sweats, pleuritic chest pain, headache, and myalgias are also less common in the elders with CAP compared to changes in mental status.[64,65] This characterization holds true as well for elders residing in long-term care facilities, even in those with severe pneumonia.[66,67] The presence of tachypnea with CAP increases with age.

In the U.S., *Streptococcus pneumoniae* is the most common cause of CAP in community-dwelling elders.[65,68,69] *Haemophilus influenzae*, *Legionella pneumophila*, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and less commonly Gram-negative bacilli are also causative pathogens. Elders residing in long-term care facilities are susceptible to pneumonia from the same organisms but also to *Staphylococcus aureus*, Gram-negative bacilli including *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*, and anaerobes, the latter occurring in the context of aspiration.[66,67] Pneumonia due to multidrug-resistant organisms such as MRSA and Gram-negative bacilli varies among elderly long-term care facility populations.[66,67,70] Elders over 75 years have a 15-fold higher incidence of pneumonia due to influenza than young adults.[68] Other respiratory viruses commonly associated with pneumonia in the elderly include human metapneumovirus (hMPV), parainfluenza virus, respiratory syncytial virus, and rhinovirus.[69]

Elders presenting to the ED with fever, tachypnea, or any clinical suspicion for pneumonia should undergo chest radiography. However, the accuracy of radiography may be limited in the face of poor functional status, early pneumonia, or immunocompromise, and computed tomography of the chest may have increased utility.[71] In addition to standard laboratory tests, patients requiring hospitalization, particularly to an intensive care unit, should have two blood cultures drawn prior to the administration of antimicrobials to guide definitive therapy.[72] Pneumococcal and *Legionella* urinary antigen testing can further aid in determining the etiology of pneumonia. Severity-of-illness scores taking into account epidemiologic, clinical, and diagnostic factors can help identify elders at high risk for mortality with CAP and inform admission decisions. The Pneumonia Severity Index (PSI) has been evaluated in elders and in EDs as a strategy for identifying low risk patients with CAP who can be safely treated as outpatients (Table 2).[73–76] The CURB-65 score (**C**onfusion, **U**remia, blood urea nitrogen >7 mmol/L or 20 mg/dL; **R**espiratory rate ≥30

breaths/min; **B**lood pressure, systolic <90 mmHg or diastolic ≤60 mmHg; Age ≥**65** years) has also been validated in older adults presenting with CAP (Table 3).[77,78] No difference in overall test performance has been identified between PSI, CURB-65, or CRB-65 (which excludes laboratory testing to assess for uremia).[79] These scores incorporate age as a primary variable; therefore, increasing age translates to greater predicted mortality risk. In the end, clinical judgment taking into account comorbid illness, new supplemental oxygen requirements, the inability to take oral medications, patient safety, and other social considerations also factor into ED decision-making regarding hospitalization for CAP.[80]

In accordance with current guidelines, empiric outpatient antimicrobial therapy for CAP in healthy elders should consist of a macrolide (*e.g.*, azithromycin, clarithromycin) for a minimum of five days, although doxycycline is also acceptable.[72] Those with comorbidities including chronic cardiac, pulmonary, hepatic, or renal disease, diabetes mellitus, malignancy, or immunosuppression should be treated with a respiratory fluoroquinolone (*e.g.*, levofloxacin) or a combination of a β-lactam (high-dose amoxicillin or amoxicillin-clavulanate) and a macrolide. The patient should be afebrile for 48 to 72 hours and demonstrate signs of clinical improvement before antimicrobials are discontinued. Elders requiring hospital admission should receive an intravenous β-lactam (*e.g.*, ceftriaxone, cefotaxime) and a macrolide. Empiric antimicrobial coverage for critically-ill patients should be expanded to cover *Pseudomonas* infection using a combination of an antipneumococcal, antipseudomonal β-lactam (*e.g.*, cefepime, piperacillin-tazobactam, meropenem) and either azithromycin or a fluoroquinolone. Additional coverage for MRSA may consist of either vancomycin or linezolid. The decision to empirically treat for multidrug-resistant organisms such as MRSA or Gram-negative bacilli should take into account the severity of disease and individual risk factors including prior antibiotic treatment and recent hospitalization. Much debate surrounds the concept of healthcare-associated pneumonia (which includes elders residing in long-term care facilities, those hospitalized ≥2 days in the preceding 3 months, those receiving home infusion therapy or domiciliary wound care, and those who have received hemodialysis in the past month) and its ability to identify patients at risk for CAP due to multidrug-resistant organisms.[81] Timely administration of antimicrobials (within 4 hours of hospital arrival) for CAP has been associated with reduced in-hospital mortality, 30-day mortality, and length of stay among Medicare patients older than 65 years.[82]

The 30-day mortality for elders with CAP ranges from 0.4–2% in outpatients to 12.5–15% in those requiring hospitalization.[61,83] Mortality may be higher in nursing home residents due to advanced age, multiple comorbidities, and poor functional status compared to community dwelling elders.[66] Predictors of mortality include advanced age (≥90 years), impaired consciousness, anemia, pleural effusion, and multilobar infiltrates.[84] Specific comorbid illnesses including hip fracture, COPD, and cerebrovascular disease also adversely impact 30-day mortality.[85] Elders diagnosed with CAP often have a prolonged recovery, particularly if a history of COPD is present.[86] Given the significant burden of pneumonia among the elderly, pneumococcal and influenza vaccination are important disease prevention strategies in this high-risk population.

## Urinary tract infection

Urinary tract infections (UTI) including cystitis and pyelonephritis comprise almost 5% of all ED visits made annually by adults over the age of 65 years in the U.S.[87] In a cohort of community-dwelling elderly women, the prevalence of UTI was 16.5%.[88] Among the women over 85 years of age, almost 30% had been diagnosed with a UTI in the preceding year and 60% in the preceding 5 years.[89] In community-dwelling elderly men, the incidence of UTI increases significantly with each decade after age 60 years but remains less than half that of women through the eighth decade of life.[90,91] After pneumonia, UTI is the second most common infectious disease for which elders are hospitalized.[5,6] Increased post-void residual volume, decreased average and peak urinary flow rates, and a reduction in voided urine predispose the elder to urinary stasis, setting up conditions conducive to bacterial colonization, multiplication, and infection of the aging urinary tract. Neurogenic bladder resulting from stroke, Alzheimer's disease, and Parkinson's disease, as well as urinary outlet obstruction due to prostatic hypertrophy in men can further impair effective bladder emptying. Periurethral bacterial colonization in post-menopausal women, chronic prostatitis in men, and infected renal or bladder calculi can serve as reservoirs for triggering recurrent UTIs. Among elders over 85 years of age, recent UTI, urinary incontinence, frequent falls, cognitive impairment, the inability to perform activities of daily living, and recent delirium are all predictors of UTI.[89,92]

Elders with UTI are more likely to present to the ED with altered mental status rather than fever or classic urinary symptoms such as dysuria, frequency, or urgency.[93] However, when present, acute dysuria is more specific for UTI than urinary frequency or urgency.[94] In a retrospective study, more than a quarter of elders over the age of 70 years eventually diagnosed with bacteremic UTI initially presented with confusion.[95] Nearly as many presented with cough or shortness of breath. Compared to younger women, post-menopausal women more frequently endorse non-specific symptoms including urinary incontinence, lower abdominal pain, lower back pain, chills, constipation, or diarrhea, rather than voiding symptoms.[96] Other non-localizing symptoms may include loss of appetite, nausea, vomiting, or falls. Atypical presentations including altered mental status and gastrointestinal symptoms also abound in elders with pyelonephritis, but fever and chills are more consistently present.[97] Up to a third of elders with pyelonephritis may complain of flank pain and half may have costovertebral angle tenderness on examination.

*Escherichia coli* remains the most common etiology for UTI in the elderly, followed by *Enterococcus*, *Proteus mirabilis*, and *Klebsiella pneumoniae*.[88,96,98,99] Group B streptococcus (*Streptococcus agalactiae*), *Staphylococcus saprophyticus*, *Providencia stuartii*, and *Pseudomonas aeruginosa* are also more frequent causes of UTI in the elderly than younger adults. Laboratory evaluation of UTI in the ED should consist of a urinalysis performed on a clean-catch urine specimen followed by urine culture if positive. Urine tests can be challenging to interpret due to contamination by periurethral flora and the increased prevalence of asymptomatic bacteriuria in elders. For this reason, urine tests are most helpful in ruling out rather than establishing the diagnosis of UTI in the ED. A negative leukocyte esterase and nitrite test has a negative predictive value of 100% for UTI in nursing home residents suspected to have this diagnosis.[100] In elderly women, the presence of pyuria (≥10

white blood cells/high power field) in combination with a positive leukocyte esterase and/or nitrite test has been shown to have a sensitivity of 84.8%, specificity of 81.6%, and positive predictive value of 47.2% for UTI.[88] Catheterized urine specimens yielded a lower proportion of false positive urinalyses (31%) compared to clean catch (48%) in one study of elderly women treated in the ED.[101] Urine cultures can also be problematic to interpret as infected elders may exhibit lower bacterial colony counts [$10^2$ to $10^3$ colony forming units (CFU) per mL] compared to the traditional cutoff for younger adults ($10^5$ CFU/mL).[102]

One approach to deciding when to start antimicrobial therapy for UTI in elderly women in outpatient settings hinges upon the presence of at least two of the following: fever (>38°C), clinical symptoms (acute dysuria, frequency, dysuria, suprapubic pain, costovertebral angle tenderness), pyuria, or a positive urine culture.[103] Asymptomatic bacteriuria should not be treated with antimicrobials. Though not intended specifically to address post-menopausal women, current guidelines for the management of UTI in adult women recommend trimethoprim-sulfamethoxazole (TMP-SMX) as first-line empiric therapy if local resistance rates for pathogens causing cystitis are <20%.[104] Nitrofurantoin has also been endorsed for the treatment of cystitis in women and can be used in elders depending on creatinine clearance and their capacity to recognize signs of pulmonary toxicity.[103] Fluoroquinolones should be reserved for complicated infections (*e.g.*, pyelonephritis). For men, either TMP-SMX or a fluoroquinolone should be used to treat UTI. A short course of antimicrobial therapy (3–6 days) is appropriate for treating uncomplicated cystitis in elderly women.[105] Longer durations totaling seven to fourteen days are recommended to treat pyelonephritis and any UTI in an elderly man.[104] Significant resistance to fluoroquinolones and other antimicrobials have been documented in elderly community-dwelling and long-term care facility populations alike, due in part to widespread and sometimes lax use of antimicrobials.[87,91,98,99,106,107] Antibiograms detailing local antimicrobial resistance patterns for common urinary pathogens can help inform appropriate empiric therapy in the ED. Likewise, close outpatient follow-up to assess for clinical improvement and review of the appropriateness of empiric antimicrobial therapy based on urine culture results can help tailor further management.

While most elders with UTI will be treated as outpatients, those with severe UTI including associated bloodstream infection will require hospitalization and intravenous antimicrobial therapy. Predictors of severe UTI include the presence of fever, altered mental status, hemodynamic instability, leukocytosis, and end-organ dysfunction.[108,109] In-hospital mortality among elders with bacteremic UTI may be as high as 30%.[109] Therefore, hospitalized elders with severe UTI and emerging sepsis should receive broad-spectrum antimicrobial therapy pending urine and blood cultures.

## Central nervous system infection

While the incidence of bacterial meningitis among adults in the U.S. has declined since the introduction of the *Haemophilus influenzae* type B and pneumococcal conjugate vaccines over the past quarter century, mortality associated with this disease remains over 20% in those aged 65 years and over.[110] *Streptococcus pneumoniae* is the leading cause of bacterial meningitis in elders while meningitis due to *Neisseria meningitidis* or *Haemophilus*

*influenzae* is relatively uncommon. *Listeria monocytogenes*, group B *Streptococcus*, and Gram-negative bacteria (*e.g.*, *E. coli*, *K. pneumoniae*) can be causative pathogens in this population.[110–115] Predisposing conditions such as otitis, sinusitis, or pneumonia may be present and sepsis may complicate up to a third of cases.[112,114–116] Elders may have fever, headache, or neck stiffness, but more commonly exhibit altered mental status, seizure, stupor, or coma.[111–117] Abnormal neurological findings are often present, including focal motor deficits, cranial nerve abnormalities, and aphasia.[115,117] Kernig's and Brudzinski's signs may be absent or unreliable as osteoarthritis, degenerative disc disease, and movement disorders (*e.g.*, Parkinson disease) can render such maneuvers difficult to execute, much less interpret. Lumbar puncture should be strongly considered as part of the standard evaluation for mental status change in the elderly, even if the patient is afebrile. Computed tomography (CT) of the head prior to lumbar puncture is a prudent step in evaluating the elder with fever and altered mental status given the risk for an intracranial mass lesion (*e.g.*, brain abscess, malignancy, or hematoma). Cerebrospinal fluid (CSF) analysis generally reveals a pleocytosis (>10 white blood cells/mm3) and a culture of the CSF should be obtained. Empiric antibiotic therapy for bacterial meningitis in the elderly should consist of intravenous vancomycin and a third-generation cephalosporin (*e.g.*, ceftriaxone) with expanded coverage for *L. monocytogenes*, usually intravenous ampicillin, pending finalization of the CSF culture.[118] If a lumbar puncture cannot be performed expediently, empiric antimicrobial therapy should be initiated without further delay given the high mortality associated with bacterial meningitis. Adjuvant corticosteroid therapy has been associated with fewer neurological sequelae across all types of bacterial meningitis (RR, 0.83; 95% CI, 0.69 to 1.0) and reduced mortality in *S. pneumoniae* meningitis (RR, 0.84; 95% CI, 0.72 to 0.98) based on analyses of existing randomized controlled trials.[119]

Viral encephalitis should be a part of the differential diagnosis of any elder presenting with altered mental status or behavioral change. Herpes simplex encephalitis (HSE) due predominantly to herpes simplex virus type 1 is one of the most common forms of sporadic fatal encephalitis worldwide, accounting for 10–15% of all viral encephalitis cases.[120] Often encountered in the elderly,[121,122] HSE can manifest with fever, headache, language difficulties, memory impairment, behavioral or personality changes, psychosis, or seizures. Cerebrospinal fluid analysis may reveal pleocytosis or hemorrhage, but can also be acellular in up to 15% of patients early in the course of disease.[123–125] While polymerase chain reaction (PCR) of the CSF is highly sensitive (>95%) and specific (>99%) for HSV,[120] it too can be negative in the early stages of disease.[123,126] In situations where the clinical suspicion for HSE is high, repeat lumbar puncture in 3–7 days to obtain CSF for HSV PCR may be warranted to safely exclude the diagnosis.[120] Temporal and/or inferior frontal lobe edema and hemorrhage characteristic of HSE is best visualized with magnetic resonance imaging (MRI) of the brain; bilateral temporal lobe involvement is a late but pathognomonic finding. Advanced age, depressed level of consciousness, prolonged duration of symptoms prior to presentation, extensive brain involvement on MRI, and delayed antiviral therapy (>2 days) have all been associated with poor outcomes in HSE.[123,127,128] Without appropriate antiviral therapy, mortality from HSE historically approaches 70%.[129] Therefore, empiric intravenous acyclovir should be initiated in an elder with suspected encephalitis while awaiting the results of the HSV PCR to evaluate for HSE.[120] Adjusted dosing may be

necessary in the setting of renal insufficiency to prevent acyclovir-induced crystalluria and nephrotoxicity.

## Skin and soft tissue infections

Atrophy and reduced elasticity, turgor, and perfusion render aging skin prone to tears and pressure ulcer formation, particularly in the setting of comorbid diabetes mellitus, peripheral vascular disease, and impaired mobility. Decreased skin turnover and malnutrition contribute to delayed wound healing. Compromised skin serves a portal of entry for *S. aureus*, *Streptococcus* species, and other bacteria leading to infections of the skin and soft tissues. Venous stasis and lymphedema, often following surgical disruption of the lymphatics during saphenous vein harvesting or axillary node dissection, can also increase the risk for cellulitis and erysipelas. The incidence of lower extremity cellulitis has been shown to increase by 43.8% per 10-year increment in age, and up to a fifth of patients will experience a recurrence of cellulitis within 2 years.[130] Skin and soft tissue infections (SSTI) are particularly common in elderly long-term care facility populations.[131] The presence of skin erythema, induration, fluctuance, and purulent wound drainage help distinguish between purulent (furuncles, carbuncles, abscess) and non-purulent (cellulitis, erisypelas, necrotizing infection) SSTIs.[132] In patients with a chronic wound, increasing pain may be a helpful sign of infection but its absence does not rule it out.[133] Pain out of proportion to physical findings has long been a hallmark of necrotizing infection. Systemic toxicity manifest as fever, confusion, functional decline, and hypotension may be more indicative of severe infection as well.

Current guidelines recommend treatment of mild purulent infections with incision and drainage alone. In moderate infections, this should be accompanied by empiric antimicrobial therapy with either TMP-SMX or doxycycline to cover *S. aureus*, particularly MRSA, for five to seven days.[132] In moderate to severe infections requiring hospitalization, empiric intravenous vancomycin, daptomycin, linezolid, telavancin, or ceftaroline can be substituted instead. For non-purulent infections, typically attributable to *Streptococcus*, oral antimicrobial therapy for mild cases can consist of penicillin VK, a cephalosporin (*e.g.*, cephalexin), dicloxacillin, or clindamycin for at least five days. Moderate infections should be treated with intravenous penicillin, ceftriaxone, cefazolin, or clindamycin. Severe infections warrant emergent surgical evaluation for potential necrotizing disease in tandem with empiric intravenous vancomycin and either piperacillin/tazobactam or a carbapenem. Infected pressure ulcers are a source of increased mortality among elders.[134] Necrotizing soft tissue infections involving the fascia and muscle likewise bear high mortality, particularly in those who develop early organ dysfunction.[135]

## Expanding infectious disease considerations in the elderly

Elders are at risk for a remarkable diversity of infection beyond the major disease entities discussed in this review. From endocarditis involving native and prosthetic heart valves to musculoskeletal infections including septic arthritis and prosthetic joint infections, advances in medicine have not only extended life but increased opportunities and expanded niches for infections to take root. Pressure ulcers and diabetic foot wounds can progress to debilitating osteomyelitis. Vertebral osteomyelitis, often masquerading as chronic back pain, can simmer

undiagnosed until neurologic compromise. Repetitive antimicrobial exposure can predispose to devastating and recurrent *Clostridium difficile* infection and increases the potential for colonization and future infection with multidrug-resistant organisms. Immunocompromised states, whether from human immunodeficiency virus infection or intentional immunosuppression for malignancy, transplantation, or autoimmune disease, significantly expand the differential diagnosis in the elder presenting with fever to the ED to include a long list of unusual bacterial, viral, fungal, and parasitic diseases. Healthy as well as chronically ill elders returning from holiday abroad can bring back a wide range of tropical and vector-borne diseases in a world that has become increasingly smaller thanks to commercial air travel. While traditionally regarded as inpatient consultants, infectious disease specialists can be a valuable resource to emergency physicians charged with the care of the infected elder not only in expanding the diagnostic evaluation but assisting with appropriate selection of empiric antimicrobial therapy.

## Conclusion

Aging sets the stage for an increased predisposition to infection through waning immunity and declining anatomic and physiologic defenses against pathogens. Atypical presentations for infectious diseases are commonplace, even in severe infection. As our population ages, elders will increasingly turn to the ED for timely and comprehensive care of acute illness. With increased vigilance and armed with a deeper understanding of the unique aspects of infection in this complex patient population, emergency physicians can play an integral part in the early recognition and appropriate management of a wide spectrum of infectious diseases in the elderly, including sepsis, pneumonia, UTI, central nervous system infections, and skin and soft tissue infections, thereby reducing morbidity and mortality and optimizing patient outcomes.

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## Synopsis

With age comes an increased predisposition to infection. Waning immunity and declining anatomic and physiologic defenses render the elder vulnerable to a wide range of infectious diseases, including but not limited to sepsis, pneumonia, urinary tract infections, central nervous system infections, and skin and soft tissue infections. Clinical presentations are often atypical and muted, favoring global changes in mental status and function over febrile responses or localizing symptoms. This review encompasses the early recognition, evaluation, and appropriate management of these common infections specifically in the context of elders presenting to the Emergency Department. With an enhanced understanding and appreciation of the unique aspects of infections in the elderly, emergency physicians can play an integral part in reducing the morbidity and mortality associated with these often debilitating and life-threatening diseases.

**Key points**

1. Infectious diseases are responsible for significant morbidity and mortality among elders.
2. Immunosenescence, declining physical barriers to pathogens, and mounting medical comorbidities increase an elder's vulnerability to a wide range of infections.
3. Atypical clinical presentations of infection are common in the elderly.
4. Timely recognition and appropriate empiric antimicrobial therapy for infectious disease can increase survival and optimize clinical outcomes.

## Table 1

### Sepsis definitions

Data from Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med.* 2013;41(2):580–637

| | |
|---|---|
| **Sepsis** | Infection (documented or suspected) + some of the following SIRS criteria*:<br>• Fever (>38.3°C or 100.4°F) or hypothermia (<36°C or 96.8°F)<br>• Tachycardia (heart rate >90/min)<br>• Tachypnea (>20 breaths/min)<br>• Leukocytosis (WBC count >12×$10^3$/μL), leukopenia (WBC count <4×$10^3$/μL), or bandemia (>10%) |
| **Severe sepsis** | Sepsis-induced tissue hypoperfusion or organ dysfunction as evidenced by any of the following:<br>• Sepsis-induced hypotension<br>○ SBP <90 mmHg<br>○ MAP <70 mmHg<br>○ SBP decrease >40 mmHg or <2 standard deviations below normal for age in the absence of other causes of hypotension<br>• Lactate above upper limits of normal<br>• Urine output <0.5 mL/kg/hr for more than 2 hours despite adequate fluid resuscitation<br>• Acute lung injury with $PaO_2/FiO_2$ < 250 in the absence of pneumonia<br>• Acute lung injury with $PaO_2/FiO_2$ < 200 in the presence of pneumonia<br>• Creatinine >2.0 mg/dL<br>• Bilirubin >2.0 mg/dL<br>• Platelet count <100×$10^3$/μL<br>• Coagulopathy (international normalized ratio >1.5) |
| **Septic shock** | Severe sepsis + sepsis-induced hypotension unresponsive to fluid resuscitation (30 mL/kg of crystalloid) |

MAP = mean arterial pressure; SBP = systolic blood pressure; SIRS = systemic inflammatory response syndrome; WBC = white blood cell

*Additional general, inflammatory, hemodynamic, organ dysfunction, and tissue perfusion variables used as diagnostic criteria for SIRS can be found in the most recent update of the Surviving Sepsis Campaign guidelines.[38]

## Table 2

### Pneumonia Severity Index (PSI)[73]

Adapted from Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med.* 1997;336(4):243–250; with permission.

| Characteristic | Points |
|---|---|
| Demographic factors | |
| Age (years) | |
| Men | Age |
| Women | Age – 10 |
| Nursing home residence | + 10 |
| Coexisting illness | |
| Malignancy (active) | + 30 |
| Liver disease | + 20 |
| Congestive heart failure | + 10 |
| Cerebrovascular disease | + 10 |
| Chronic kidney disease | + 10 |
| Physical examination findings | |
| Altered mental status | + 20 |
| Respiratory rate ≥30 breaths/minute | + 20 |
| SBP <90 mmHg | + 20 |
| Temperature <35°C (95°F) or ≥40°C (104°F) | + 15 |
| Pulse ≥125 beats/minutes | + 10 |
| Laboratory and radiographic findings | |
| Arterial pH <7.35 | + 30 |
| BUN ≥11 mmol/L or 30 mg/dL | + 20 |
| Sodium < 130 mmol/L | + 20 |
| Glucose ≥14 mmol/L or 250 mg/dL | + 10 |
| Hematocrit <30% | + 10 |
| $PaO_2$ <60 mmHg | + 10 |
| Pleural effusion on chest radiograph | + 10 |

| Total Points | Risk Class | Treatment options |
|---|---|---|
| No comorbidities | I | Outpatient therapy |
| ≤70 | II | Outpatient therapy or brief hospitalization |
| 71 – 90 | III | |
| 91 – 130 | IV | Hospitalization |
| >130 | V | |

BUN = blood urea nitrogen; DBP = diastolic blood pressure; SBP = systolic blood pressure

## Table 3

CURB-65 Score

***Assign 1 point for each of the following elements present:***

- **C**onfusion (new disorientation to person, place, or time or based on specific mental status test)
- **U**remia (BUN >7 mmol/L or 20 mg/dL)
- **R**espiratory rate (≥30 breaths/minute)
- **B**lood pressure (SBP <90 mmHg or DBP <60 mmgHg)
- Age >**65** years

| Total | 30-day mortality risk | Treatment options |
|---|---|---|
| 0 or 1 | Low | Outpatient therapy appropriate |
| 2 | Moderate | Consider hospitalization |
| ≥3 | High | Hospitalization, consider intensive care unit |

Adapted from Lim WS, van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax*. 2003;58(5):377–382; with permission.