Sepsis in Older Adults

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INTRODUCTION

Sepsis is defined as life-threatening organ dysfunction caused by a host response to infection and represents a spectrum of disease severity ranging from bacteremia to septic shock. Septic shock is a subset of sepsis in which there is circulatory and metabolic dysfunction.¹ Sepsis is a significant burden on our society and disproportionally affects older adults.²,³ More than 60% of sepsis diagnoses are made in adults aged ≥65 years.⁴ The high rate of sepsis among the older population has important implications for our health care system, especially given that the incidence of sepsis is expected to increase with the aging of our population.⁵

EPIDEMIOLOGY

The overall rate of sepsis is increasing.⁴,⁵ Although there are several factors contributing to the increase, the aging of our population plays a significant role. Since 2004, the population of older adults aged ≥65 years living in the United States has

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KEYWORDS

- Older adults
- Sepsis
- Outcomes
- Infections

KEY POINTS

- Sepsis disproportionally affects older adults.
- Advanced age has been associated with worse outcomes.
- Older adults with infection can present atypically, making a prompt diagnosis of sepsis challenging.
- Special considerations must be given to selection and dosing of antimicrobials in older adults because of alterations in pharmacokinetics and pharmacodynamics that occur as a result of physiologic changes associated with aging.
- Goals of care should be discussed in all older adults with suspected sepsis.
increased 28% to more than 46 million in 2014 and is projected to more than double to 98 million in 2060.6

Using data from the National Inpatient Sample database, Kumar and colleagues7 estimated that the frequency of hospitalizations of patients with sepsis in the United States increased from 143 per 100,000 persons in the year 2000 to 323 per 100,000 persons in the year 2008, an increase of almost 17% annually. The largest absolute increase was seen in adults aged ≥65 years. Using the same database, Stoller and colleagues8 later found the incidence of sepsis to have increased from 346 per 100,000 persons in 2008 to 436 per 100,000 persons in 2012. The mean age of patients in the cohort was 69 years in 2008 and 68 years in 2012.7,8 In an observational study using hospital discharge data, Martin and colleagues3 determined that incidence rates of sepsis in older adults aged ≥65 years increased 20.4% faster than in those aged less than 65 years (mean increase 11.5% vs 9.5% per year, P<.001).

Sepsis also appears to be the most common reason older adults are admitted to an intensive care unit (ICU). In a prospective cohort study of older adults with a mean age of 75 years, approximately 64% of older adults admitted to an ICU met the definition of sepsis.9

**SUSCEPTIBILITY TO INFECTION**

There are several reasons older adults are more likely to develop infections. It is well established that immune function decreases with age, also known as immunosenescence, which puts older adults at increased risk both of developing an infection and for developing an infection with a more severe and protracted course.10,11 Aging appears to reduce the body’s immune response to infection through multiple complex pathways, such as decreased cytokine production and altered expression and function of toll-like receptors. There are also changes in adaptive immunity because of thymic involution that depresses T-cell function. In addition, B cells in older adults often produce antibodies with lower affinity that reduces immunogenicity and thus the protective effects of vaccinations.10 Poor skin integrity from age-associated changes (eg, thinning and drying) increases the risk of developing skin and soft tissue infections, and swallowing difficulty, immobility, and inadequate oral care have been associated with higher rates of pneumonia.12–14 Postmenopausal women are more likely to develop urinary tract infections (UTI) because of declining estrogen levels that alter the vaginal flora and promote the colonization of the vagina with uropathogens.15,16 For older men, prostatic hypertrophy can lead to urinary retention and stasis, predisposing this cohort to UTIs.17

Common risk factors in older adults that are associated specifically with sepsis include institutionalization (eg, hospitals, postacute care facilities), instrumentation (eg, chronic indwelling urinary catheters), frailty, malnutrition, and cognitive impairment.18 In a population-based study of older adults aged ≥65 years, a diagnosis of dementia was associated with a 50% higher risk of severe sepsis (odds ratio [OR] 1.50, 95% confidence interval [CI] 1.32–1.69), after controlling for multiple factors, including age, sex, and other comorbidities.18 Residing in a long-term care facility has also been shown to increase the risk of developing severe sepsis. In a retrospective study of emergency department visits, nursing home residents were 7 times more likely to be diagnosed with severe sepsis compared with non–nursing home residents (14% vs 1.9%) and to have higher rates of ICU admissions (40% vs 21%).19

Many common comorbid diseases in older adults increase the risk of infection and subsequent sepsis, including congestive heart failure, chronic obstructive pulmonary disease (COPD), malignancies, diabetes mellitus, and chronic liver failure.20 Long-
standing diabetes mellitus can result in delayed phagocytosis with decreased clearance of yeast and bacteria by neutrophils,\textsuperscript{21} and chronic liver failure causes impairment of complement factor formation and proliferation of cellular immunity.\textsuperscript{22} Physiologic changes associated with COPD, including impaired mucociliary clearance, alveolar macrophage dysfunction, and suppressed cough mechanism significantly increase the risk for lower respiratory tract infections in older individuals.\textsuperscript{23} Frailty, a common clinical syndrome in older adults, is associated with a decline in activities of daily living (ADLs) causing a cascade of medical problems, including an increase in traumatic falls with injuries that often lead to hospitalization, thus exposing older adults to nosocomial infections.\textsuperscript{24}

**DIAGNOSTIC CHALLENGES**

Older adults with infection often present atypically, making prompt diagnosis and treatment initiation challenging. Fever, the most recognized clinical feature of infection and the most common sign associated with sepsis, is absent in approximately 30% to 50% of older adults with infection. A retrospective cohort study of patients seen in an emergency department found that more than 50% of adults aged \( \geq 65 \) with bacteremia did not present with a fever, defined as a temperature greater than 100.4°F (>38°C). In addition to bacteremia, older adults often have an absent or diminished febrile response to other infections, such as pneumonia, endocarditis, and meningitis.\textsuperscript{25–27} Several studies have shown that older adults often have a basal body temperature lower than the standard normal body temperature of younger adults.\textsuperscript{28–30} One study found the average baseline temperature of 50 hospitalized older adults aged \( \geq 65 \) years without infection to be 97.9°F (36.6°C) measured orally, substantially lower than 98.6°F (37°C), the traditionally accepted normal body temperature of younger adults.\textsuperscript{31} In 2008, The Infectious Disease Society of America proposed a new definition for fever in older adults. Specifically intended for residents of long-term care facilities, it has also been used in other clinical settings and is defined as follows:

- A single oral temperature greater than 100°F (>37.8°C); or
- Repeated oral temperatures greater than 99°F (>37.2°C); or
- Repeated rectal temperatures greater than 99.5°F (>37.5°C); or
- Increase in temperature of greater than 2°F (>1.1°C) over baseline temperature.\textsuperscript{32}

However, the definition of fever often used to determine a systemic inflammatory response to infection is >38.3°C (100.9°F). Thus, an older adult may not meet the “fever” threshold in many clinical settings.\textsuperscript{33} That being said, assessing temperature in older individuals can still provide important clinical information.\textsuperscript{34} One strategy in older adult patients is to assess the change in temperature from the individual patient’s baseline rather than the absolute temperature value.\textsuperscript{22}

Other challenges associated with diagnosing infections in older adults are atypical syndrome-specific signs and symptoms, which may require a higher clinical index of suspicion for infection.\textsuperscript{14} For example, pneumonia in older adults can present as confusion, falls, and a decrease in functional status. Although typical localizing symptoms, such as increased sputum production and cough might be absent, an increased respiratory rate and oxygen requirements, detectable via pulse oximetry, may suggest pneumonia.\textsuperscript{32,35} Recognizing dysuria, a typical feature of UTI, may be challenging in older adults because other conditions, such as prostate enlargement and genital prolapse, may cause similar sensations.\textsuperscript{36} In addition, older adults who are nonverbal may not be able to express feelings of discomfort; their caregivers may have to rely on other changes to recognize symptoms suggestive of a possible
infection. Furthermore, differentiating infection from other noninfectious causes, such as congestive heart failure and urinary incontinence, can cause diagnostic uncertainty.

Obtaining accurate clinical information and diagnostic studies can be difficult in subgroups of older individuals. Interpreting biomarkers of sepsis in older adults is challenging because other comorbid conditions can also lead to abnormal findings. For example, lactic acid level is an important marker for sepsis diagnosis and surveillance response to treatment; as its level increases, so does the mortality risk from sepsis. However, dehydration and anemia, common in older individuals, can also result in increased lactic acid levels (low red cell count and contracted volume), making it difficult at times to interpret values clinically. Collecting a urine sample that is not contaminated with skin bacteria can be challenging in a cognitively impaired individual in the acute care hospital or nearly impossible in an agitated or incontinent patient in a nursing home setting. Physical disabilities, such as kyphosis, osteoporosis, and immobility, can also make it difficult to obtain good diagnostic chest radiographs to assess for pulmonary infiltrates suggestive of a lower respiratory tract infection.

**CAUSE**

The most common infectious sources of sepsis in older adults are respiratory tract infections and genitourinary tract infections. Less common causes include skin and soft tissue infections and gastrointestinal infections, with the latter being associated with the highest mortality in older adults.

Older adults are more likely than younger adults to develop infections from gram-negative organisms. Martin and colleagues reported that older adults aged ≥65 years were 1.31 times more likely to have a gram-negative infection compared with adults under the age of 65 (95% CI, 1.27–1.35). The most common organism identified by urine culture in patients who developed sepsis from a urinary source is *Escherichia coli* (50%). Although *E coli* is the predominant cause of UTI in both younger and older adults, older adults are at increased risk for infection from other gram-negative bacteria, such as *Proteus* spp, *Klebsiella* spp, and *Pseudomonas* spp.

Common gram-positive organisms in older adults with bloodstream infections include *Staphylococcus aureus*, *Enterococci* spp, and *Streptococci* spp. In a cohort of older adults aged ≥60 with sepsis due to pneumonia, 16.9% had a positive culture for methicillin-sensitive *S aureus* and 12.3% had a positive culture for methicillin-resistant *S aureus* (MRSA).

**MANAGEMENT**

The overall management of sepsis in older adults follows the same guidelines as in younger adults and is outlined in the “Surviving Sepsis Campaign, International Guidelines for Initial Management of Sepsis and Septic Shock: 2016,” summarized in Table 1. Although the underlying principles are the same, there are a few unique considerations when managing older adults.

**Antimicrobial Selection and Dosage**

Early administration of effective antibiotic therapy is essential, because poor outcomes are associated with inadequate therapy across all ages. Older adults are at higher risk compared with younger adults for having an infection from a multidrug-resistant organism (MDRO) for multiple reasons, including the following:
Foreign bodies (e.g., urinary catheter, vascular access devices)
Recent hospitalizations (especially within 90 days)
Recent exposure to antibiotics
Residing in a long-term care facility
Comorbid conditions (e.g., COPD, renal failure, diabetes mellitus)
Prior colonization with an MDRO

In a case-control study of patients 65 years of age and older admitted to a tertiary care hospital with gram-negative bloodstream infections, 8% of these infections were caused by MDROs; initial antibiotic therapy was ineffective for more than half (63%) of these patients.\(^{44}\) In addition, in a prospective cohort study of adults with bacteremia, MRSA was more prevalent in those aged greater than 65 compared with adults aged ≤ 60 (OR, 1.66, 95% CI 1.06–2.59).\(^ {45}\) Thus, clinicians must be cognizant of the pathogens that can lead to sepsis in the older population when choosing empiric antibiotic therapy and simultaneously of the risk of developing antibiotic resistance.

The Surviving Sepsis Campaign Guidelines strongly recommend initiation of intravenous antimicrobials within 1 hour for both sepsis and septic shock (moderate quality of evidence) (Table 2).\(^ {1}\) The specific antibiotic regimen should always be modified based

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<thead>
<tr>
<th>Table 1</th>
<th>Selected initial management strategies for sepsis and septic shock</th>
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<tr>
<td>• Patients with hypoperfusion should receive at least 30 mL/kg of intravenous crystalloid within 3 h</td>
<td>Strong recommendation, low quality of evidence</td>
</tr>
<tr>
<td>• Patients should be frequently reassessed</td>
<td>Best practice statement</td>
</tr>
<tr>
<td>• Norepinephrine is the first choice for patients who need vasopressors</td>
<td>Strong recommendation, moderate quality of evidence</td>
</tr>
<tr>
<td>• For patients who require vasopressors, the target mean arterial pressure should be 65 mm Hg</td>
<td>Strong recommendation, moderate quality of evidence</td>
</tr>
<tr>
<td>• Broad-spectrum intravenous antibiotics should be started within 1 h of sepsis recognition</td>
<td>Strong recommendation, moderate quality of evidence</td>
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<tr>
<th>Table 2</th>
<th>Selected infection management strategies for sepsis and septic shock</th>
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<tr>
<td>• Empiric(^ a) broad-spectrum(^ b) therapy</td>
<td>Strong recommendation, moderate quality of evidence</td>
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<tr>
<td>• Regular assessment for narrowing antimicrobial coverage</td>
<td>Best practice statement</td>
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<tr>
<td>• Dosing of antimicrobials should be optimized based on pharmacokinetic/pharmacodynamics principles and specific drug properties</td>
<td>Best practice statement</td>
</tr>
<tr>
<td>• Obtain anatomic source control as quickly as practical after diagnosis</td>
<td>Best practice statement</td>
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\(^ a\) Initial therapy started without a definite pathogen or source.
\(^ b\) Use of one or more antimicrobials to ensure coverage of a wide range of pathogens.
on the suspected site of infection, local antibiotic susceptibility patterns, and a patient’s own microbiologic history (if available). Modification and deescalation of antibiotics once a source is identified and culture data are made available is crucial to adhering to antibiotic stewardship principles. Judicious use of antibiotics can help minimize risks of antibiotic resistance and other commonly associated negative consequences (eg, *Clostridium difficile* infection, adverse drug reactions). An understanding of the physiologic changes that occur with aging and their impact on pharmacokinetics and pharmacodynamics is critical when selecting antibiotics for older patients with sepsis.46 Drug-receptor interactions (agonist/antagonist), post-receptor drug effects (signaling and receptor regulation), and drug-drug interactions are all important concepts when dosing antibiotics in the aging population.47 Clinically, pharmacodynamics can be thought of with respect to toxicity and clinical response. Age is a well-documented risk factor for the development of both liver and kidney toxicities and should be taken into consideration when dosing antibiotics. Decreased systemic perfusion due to age-related atherosclerosis and increased peripheral vascular resistance is further magnified during sepsis.48 Physiologic changes that occur with aging can affect all stages of pharmacokinetics.49 With respect to absorption of drugs, slowed gastric emptying, increased gastric pH, and a decrease in small bowel surface area can all affect absorption rates of antibiotics.49 Furthermore, body fat and total body water decrease with aging, resulting in an increase in the volume for drug distribution within the tissues. A decrease in serum albumin, especially during critical illness, can increase serum levels of drugs that bind to albumin within the body.49,50 A decrease in the activity of the cytochrome P450 system can also contribute to slower rates of metabolism of medications that are primarily metabolized within the liver.51 Finally, decreased glomerular filtration rate (GFR) is extremely prevalent in the aging population. Antibiotics, such as vancomycin, tobramycin, and meropenem, require renal dosage adjustment to prevent toxicity.52 It is critically important that clinicians remember that even though measured levels of creatinine may technically remain within normal range, creatinine clearance is decreased because of a decrease in lean muscle mass in older individuals.53

**Sedation and Delirium**

Older critically ill adults with sepsis are at higher risk for developing delirium than younger adults because of underlying cognitive changes. Delirium has been associated with increased mortality in this population.54 In a prospective study of older adults aged greater than 60 admitted to an ICU, the number of days someone experienced ICU delirium correlated with an increased risk of death the year following that admission (HR, 1.10; 95% CI, 1.02–1.18).55 The 2016 Surviving Sepsis Guidelines recommend as a best practice statement that “continuous or intermittent sedation be minimized in mechanically ventilated sepsis patients, targeting specific titration endpoints” to reduce duration of mechanical ventilation and support earlier mobilization.1 Nonpharmacologic approaches to the management of pain, agitation, and delirium should be explored and use of benzodiazepines should be minimized.56,57

**OUTCOMES**

**Mortality**

Although advances in diagnosis and management of sepsis have led to significant improvements in outcomes across all ages, overall mortality in older adults remains high. In-hospital mortalities reported in patients aged ≥65 are around 30% to 60% and approach 40% to 80% in those aged 80 years and older.2,4,58 Several studies have
found age to be an independent risk factor for mortality,\textsuperscript{3,58} although others suggest that factors such as comorbid conditions play a more important role.\textsuperscript{4,59,60} In a retrospective study evaluating outcomes of adults admitted with severe sepsis to 171 ICUs in Australia and New Zealand, the mortality in patients without comorbidities was 14% compared with 26.4% in patients with comorbidities. In this same cohort, adults aged \( \leq 44 \) had a mortality of 7.3% compared with 30.4% in adults aged \( \geq 85 \) years.\textsuperscript{4}

The Sequential (Sepsis-related) Organ Failure Assessment (SOFA) and the quick-SOFA (qSOFA) are newly developed tools used to predict mortality in patients suspected of having sepsis.\textsuperscript{61} The qSOFA contains the following 3 components:

- Respiratory rate \( \geq 22 \) breaths per minute
- Altered mentation
- Systolic blood pressure \( \leq 100 \) mm Hg

Both the SOFA and qSOFA have been shown to be superior to the systemic inflammatory response syndrome criteria in identifying patients likely to have a prolonged ICU stay or die in the hospital.\textsuperscript{1,62,63} Although the SOFA and qSOFA have not been exclusively studied in older adults, they do not rely on fever as a clinical criterion. Further studies are needed relative to the specific applicability of these 2 tools to older adults with suspected sepsis.

**Functional Status and Cognitive Impairment**

In older adults who survive hospitalization, sepsis has been associated with a variety of other negative consequences, including decreased quality of life and new functional and cognitive impairment.\textsuperscript{64,65} A study by Iwashyna and colleagues\textsuperscript{65} identified significant changes in cognition and functional status in a cohort of older adults, with a mean age of 78, who survived sepsis. In this cohort, the percentage of patients eventually surviving sepsis with moderate to severe cognitive impairment increased from 6.1% (95% CI, 4.2\%–8.0\%) before sepsis hospitalization to 16.7\% (95% CI, 13.8\%–19.7\%) after hospitalization. Severe sepsis was found to be associated with a 3-fold higher rate of progression to moderate to severe cognitive impairment (OR 3.34, 95% CI 1.53–7.25). These patients also had a decrease in ADLs and instrumental activities of daily living (IADLs), defined as mean of 1.57 (95% CI, 0.99–2.15, \( P<.001 \)) new functional limitations in ADLs and/or IADLs in patients with no limitations before hospitalization, and a mean of 1.5 (95% CI, 0.87–2.12, \( P<.001 \)) new functional limitations in patients with mild to moderate limitations before hospitalization.

**Postacute Care**

A significant percentage of older adults with sepsis who survive hospitalization are discharged to a postacute care facility. Martin and colleagues\textsuperscript{3} found that older patients aged \( \geq 65 \) years were less likely to return home compared with younger adults aged less than 65 years (54\% vs 76\%, \( P<.001 \)) and that admission to a long-term care facility was greater in the older age group (37\% vs 15\%, \( P<.001 \)). Admission to a postacute care facility after hospitalization for sepsis appears to have remained relatively stable over the past several years, representing approximately 44.9\% of hospital discharges in 2008 and 42.6\% of hospital discharges in 2012.\textsuperscript{8}

**GOALS OF CARE**

Although there has been improvement in mortalities of sepsis over the past decade, older adults are at risk for a variety of other unwanted outcomes. As discussed earlier, older adults surviving a sepsis hospitalization often suffer decreased quality of life,
have increased functional impairments, are less likely to return home, are more likely to be rehospitalized, and have increased reliance on caregivers. Goals of care should be discussed with older adults with suspected sepsis when possible and patients’ preferences honored. An observational cohort study in adult patients admitted to a general medical service over a 2-year period found that 75% of patients in that study reported preferring to die at home, yet most (66%) died in an institutional setting. It is therefore important to engage in conversations about realistic chances of survival and to identify and discuss each patient’s potential functional status and quality of life should they survive hospitalization. Rather than offering antibiotics and other aggressive care in patients not expected to survive sepsis, palliative care services may alleviate pain and suffering and allow for a more peaceful death. The Surviving Sepsis Campaign Guidelines provide recommendations for setting goals of care in patient with sepsis:

- Discuss goals of care and prognosis with patients and families (best practice statement).
- Incorporate goals of care into treatment and end-of-life care planning, using palliative care principles where appropriate (strong recommendation, moderate quality of evidence).
- Addressed goals of care as early as feasible, but no later than within 72 hours of ICU admission (weak recommendation, low quality of evidence).

Cost Burden of Sepsis in the Elderly

According to the Agency for Healthcare Research and Quality, the annual cost of sepsis management in 2011 was $20 billion with more than 50% of this cost attributed to the care of individuals over the age of 65 years. Sepsis is regarded as the most expensive condition treated in hospitals in the United States. Furthermore, readmission as a result of sepsis is not only more likely, but also at least 2 to 3 times more costly than readmission for other medical conditions, including COPD, pneumonia, and heart failure.

SUMMARY

Identifying, diagnosing, and treating sepsis in older individuals remain a major challenge for clinicians. Physiologic aging changes and the presence of multiple comorbid conditions can be a barrier to early diagnosis and treatment. Reliance on temperature must be done in context, given that temperature response is often blunted and delayed in older adults. Although rates for surviving sepsis in older adults have improved, overall mortality remains high and older adults surviving sepsis often suffer from significant functional impairment. Further research to determine optimal diagnostic and treatment approaches to sepsis specifically in the older adult population is needed.

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