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Challenges with Diagnosing and Managing Sepsis in Older Adults

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Abstract

Sepsis in older adults has many challenges that affect rate of septic diagnosis, treatment, and monitoring parameters. Numerous age-related changes and comorbidities contribute to increased risk of infections in older adults, but also atypical symptomatology that delays diagnosis. Due to various pharmacokinetic/pharmacodynamic changes in the older adult, medications are absorbed, metabolized, and eliminated at different rates as compared to younger adults, which increases risk of adverse drug reactions due to use of drug therapy needed for sepsis management. This review provides information to aid in diagnosis as well as offers recommendations for monitoring and treating sepsis in the older adult population.

Keywords

Sepsis; elderly; antibiotic therapy; immunosenescence; inflammation; vasopressor therapy

Introduction

Older adults are at an increased risk of contracting infectious pathogens due to their declining immune system, in addition to other age-related changes throughout all body systems¹. Due to these vulnerabilities, older adults are at an increased risk of sepsis¹. Often, diagnosis and initiation of sepsis bundles are delayed due to the abnormal infectious disease presentations in older adults. In the most recent Surviving Sepsis Campaign (SSC) 2012 Guidelines, there are recommendations on when to initiate antibiotics, fluid resuscitation, and vasopressors². However, there are not any recommendations specifically designed for older adults. For the treatment of septic shock syndrome, limited literature exists to guide appropriate selection and dosing of pharmacotherapy in older adults. Many clinical trials of adult patients with severe sepsis and septic shock include a large proportion of older adults, ranging anywhere from 30–45% of the study population, and most enroll patients with an average age of 65 years, suggesting results could be applicable to the older adult population. However, there is a paucity of published data evaluating the effects of vasoactive therapies and overall outcomes specific to patients of advanced age to be able to make practice recommendations. Selection of specific vasopressor and inotropic medications is largely guided by expert opinion, clinician preference for individualization of hemodynamic parameters, and minimization of adverse effects such as tachycardia and new-onset arrhythmias^{3–5}. As the older adult population continues to grow, treating sepsis will become a more costly endeavor as hospital costs currently exceed \$60 billion dollars per year⁶. There are many challenges to treating and diagnosing older adults with sepsis, in addition to the inability for older adults to combat against infectious pathogens. The purpose of this expert review is to identify age-related changes which increase the risk of sepsis and cause difficulty with diagnosis and to provide recommendations for treating sepsis in older adults.

Geriatric Specific Factors

Immunosenescence

Age-related changes in the immune system, otherwise known as immunosenescence, increase the vulnerability of the older adult to contract an infection but decrease the older adults' immune response⁷. There are multiple, complex factors that contribute to immunosenescence and increase the risk of older adults in acquiring sepsis⁸. Table 1 includes additional factors that may contribute to predisposing factors for sepsis in older adults.

Overall decrease in T cell counts is a marker for immunosenescence⁹. Thymal involution occurs as the older adult ages which not only leads to decreased thymal mass, but also decreased output of naïve T cells^{9,10}. These factors decrease the number of T cells which cause a decrease in interleukin-2 (IL-2) activation, secretion and proliferation effects to activate lymphocytes¹⁰. With the activation of lymphocytes delayed and blunted, it is challenging for the immune system to eradicate invading pathogens.

An additional factor of immunosenescence is the decreased numbers of B cells and the reduced production of antibodies¹¹. Antigen-experienced B cells are overproduced due to the response to the presence of environmental or autoantigens, whereas naïve follicular B-

cell production is diminished^{8,11}. Older adults are at higher risks of contracting infectious caused by more invasive pathogens. These pathogens include *Listeria monocytogenes*, West Nile virus, and severe acute respiratory syndrome virus¹². The decreased amounts of naïve B cells are unable to cope and respond to the new antigens. T helper cells are mostly absent in older adults due to the lack of expression of costimulator molecules, which are needed for the interaction of T cells activating B cells as a part of humoral adaptive immunity^{1,13}. Due to the impairment in the T helper cells and decreased amount of naïve B cells, the immune system is unable to mount a response to newer antigens including vaccinations.

Another factor is that older adults appear to be in a chronic low-grade proinflammatory state. There is debate on if there is one major cause of the proinflammatory state—whether it is solely due to atherosclerosis, or if there is reactivation of viral illnesses^{14–16}. Older adults have increased concentrations of interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-alpha), and C-reactive protein (CRP)¹⁷. These inflammatory factors circulate through the bloodstream and may then blunt and delay the overall immune response through down-regulation of receptors¹⁸. A new term, *inflammaging*, has been introduced to describe this chronic, low-grade, inflammation that occurs in older adults. In addition to CRP and IL-6, older adults also have increased levels of other interleukins, especially interleukin-10 (IL-10). In severe sepsis, older adults have exhibited a larger ratio of IL-10 compared to TNF, which has been associated with increased mortality^{1,20}.

Additional age-related changes in other systems may increase the older adults' risk of infection. Within the respiratory system, there is a decreased reserve lung capacity, reduced cough reflex to clear bacteria by expectoration, and reduced respiratory muscle endurance²¹. Older adults experience a decrease in circulating thyroid hormone levels. Decreasing thyroid hormone levels have been linked to decrease in natural killer cell activity, which provides additional rationale for the blunting of the immune response to novel antigens^{7,22}. With all of these factors affecting immunosenescence, older adults are at an elevated risk of infection.

Diagnostic Challenges

Diagnosis of sepsis in older adults can be especially difficult and often goes under-diagnosed²³. Older adults with sepsis often present with atypical, nonspecific symptoms. The most common example is the presence of altered mental status, which is a nonspecific marker of infection in older patients and does not necessarily indicate a nervous system infection as it would in younger adults. Other examples of unique symptoms of infection in older patients include: lethargy, tachypnea, loss of appetite, dehydration, weakness, dizziness, falls, and incontinence^{7,23,24}. Finally, due to the presence of multiple comorbid conditions and an increased incidence of delirium in this patient population, it can be challenging to acquire a thorough history of present illness that would normally assist in the initial diagnosis of infection²⁵.

When looking at a disease-specific diagnosis, there are several important diagnostic considerations that are unique to older adults. For example, older adults with bacteremia, may not present with the typical signs of fever and chills²⁵. Older adults with urinary tract infections often present with confusion and they are less likely than younger adults to

present with the classic symptoms of urinary frequency and pain²⁵. Moreover, older adults with pneumonia are more likely to present with generalized weakness, falls, and hypoxemia, rather than the typical symptoms of fever and chest pain^{7,25}.

While symptoms may be unreliable indicators of infection in these patients, biomarkers such as erythrocyte sedimentation rate, CRP, lactate, and procalcitonin still play an important diagnostic role. These biomarkers may be elevated at baseline due to increased age and the presence of multiple disease states. As a result, clinicians should assess these biomarkers relative to the patient's previous findings, or baseline levels, and be alert to extremely elevated values²⁵. Clinicians should anticipate potential issues when checking these values, as it may be difficult to obtain adequate laboratory tests and cultures in patients who are frail and have cognitive decline¹.

Sepsis, as a syndrome of inflammatory response to infection, is typically diagnosed using the systemic inflammatory response syndrome (SIRS) criteria. The typical signs of sepsis and the SIRS criteria are not commonly seen in geriatric patients²⁵. One notable example is the difficulty in assessing the SIRS criteria of temperature ($>38^{\circ}$ or $<36^{\circ}$ C). The underlying problem assessing temperature in older adults is the fact that the body's baseline temperature changes with age and can often times be $0.6\text{--}0.8^{\circ}$ C lower in older adults than in younger adults²⁶. Additionally, there is a decreased temperature response to infection as a result of decreased cytokine production, decreased sensitivity of the hypothalamus to cytokines, and poor peripheral thermoregulation⁷. Malnutrition also leads to a decreased temperature response to infection⁷. As a result of all of these factors, older adults may have a more blunted effect on temperature response to infection, meaning that patients with infection could be less likely than younger adults to present with the typical sign of fever²⁵.

It is still important to assess temperature in these patients, as it may provide important clinical information. In fact, one study found that, in addition to shaking chills, an elevated temperature was a good predictor of bacteremia in patients over the age of 80 years old²⁷. Additionally, it may be advantageous to assess the change in temperature from the individual patient's baseline rather than the absolute temperature value in older adult patients⁷.

Comorbid Conditions

Many common comorbidities in older adults may also increase the risk of infection. The most common comorbidities that have been linked to an increase risk of infection are congestive heart failure, chronic kidney disease, diabetes mellitus, chronic liver failure, chronic obstructive lung disease, malignancies, and chronic infections²⁸. Chronic diabetes mellitus not only increases infection risk due to formation of neuropathy and poor vasculature from longstanding history of the disease, but it also leads to delayed phagocytosis corresponding with decreased clearance of yeast and bacteria by the neutrophils²⁹. Chronic kidney disease is also thought to cause similar impairments on the immune system as diabetes mellitus³⁰. Iron overload inhibits cellular immune effector function, which is commonly seen in chronic kidney disease due to potential over supplementation of iron for treatment of anemia of chronic disease³¹. Chronic liver failure causes impairment of complement factor formation and proliferation of cellular immunity⁷.

As older adults are likely to have multiple comorbidities, they are at a further increased risk of infections.

Comorbidities may also mask or delay sepsis diagnosis. Serum lactate levels are considered to be the most used biomarker for diagnosis of sepsis³². Lactate development does occur during anaerobic metabolism, which is caused by hypoperfusion of end organs. As lactate levels increase, so does the mortality risk due to sepsis. Comorbidities, such as anemia and severe dehydration, can increase lactate levels due to lack of red blood cells and fluid³³. As many older adults may have anemia and are likely to not remain adequately hydrated, there may be a risk of increased serum lactate levels; however, it is still recommended to obtain lactate levels in settings where sepsis may be caused by pneumonia or if there is a delayed time to achieve clinical stability³³.

Pharmacodynamic/Pharmacokinetic Challenges

When evaluating the use of pharmacotherapy, it is first important to consider the number of changes that can be seen in the absorption, distribution, metabolism, and elimination of drugs in older adults.

Absorption of medications may decline in older adults. Atrophy of the gastric parietal cells increases gastric pH, which may alter the absorption of medications that are dependent on gastric acidity^{34,35}. Delayed emptying time leads to a decreased rate of absorption and a decreased drug peak concentration, another problem in older adults^{34,35}. These patients have a decreased intestinal surface area and decreased abdominal blood flow which may limit systemic drug absorption^{34,35}.

Older adults tend to have altered body composition as lean muscle mass decreases and body fat increases^{7,35}. Total body water also decreases an estimated 10–15% as patients age from 30 to 90 years old³⁵. This leads to a decreased percentage of total body water and an increased concentration of adipose tissue and leads to a decreased volume of distribution for hydrophilic medications and an increased volume of distribution for lipophilic medications⁷. Older adults also have decreased serum albumin leading to an increased concentration of free fraction of drugs which are normally highly protein bound⁷.

There are important changes in the way older adults metabolize and eliminate medications. Age-related decline in hepatic blood flow and impairment in hepatic enzymes lead to decreased first-pass effects and increased half-lives of hepatically cleared medications^{7,34}. Renal function is difficult to estimate in older patients due to an age-related decrease in muscle mass, but also age-related damage to glomeruli decreases renal filtration capacity⁷. This can lead to decreased clearance of electrolytes and renally cleared medications. It is important to consider how age influences the typical pharmacokinetic/pharmacodynamic profile of antimicrobial agents in older adults and to avoid using standard adult dosing nomograms³⁴.

Pharmacokinetic changes ultimately have variable implications on the treatment of sepsis and must be weighed heavily before initiating therapy. For instance, older adults tend to have decreased systemic perfusion³⁶. This is a result of atherosclerosis and increased

peripheral vascular resistance, and this effect may be increased in cases of sepsis^{7,36}. Ultimately, medications have decreased penetration into tissue and contribute to sub-therapeutic concentrations of drug leading to a higher incidence of treatment failure⁷. Alternatively, due to decreased perfusion to the liver and kidneys, metabolism and elimination of antimicrobials may be decreased leading to increased risks of various toxicities³⁶. Older adults with multiple comorbidities, are susceptible to polypharmacy, which may pose additional risks of ADRs³⁴.

Considerations of Sepsis Treatment in Older Adults

Fluid Resuscitation and Hemodynamic Support

Initial resuscitation of the septic patient should be achieved within 6 hours of triage using a protocol-based process². Protocol-based resuscitation is associated with improved mortality outcomes in older adults and places emphasis on early, aggressive administration of adequate intravenous (IV) fluids³⁷. This strategy serves to optimize cardiac preload and to improve or preserve organ perfusion pressure until other hemodynamic targets are met³⁸. Patients should initially receive a 30 mL/kg IV fluid challenge followed by additional fluid therapy until the patient no longer demonstrates hemodynamic improvement. Though patients are likely at greater risk of under-resuscitation, some caution should be taken to avoid excessive resuscitation, particularly in patients with known heart failure or significant renal impairment.

The administration of vasoactive agents is recommended to improve and preserve sepsis-induced end-organ perfusion for patients with septic shock exhibiting life-threatening hypotension. Mean arterial pressure (MAP) is the driving pressure for peripheral blood flow and serves as the therapeutic target for all patients with sepsis-induced end-organ hypoperfusion. The SSC guidelines provide a strong recommendation to reverse hypotension for patients with septic shock, characterized by arterial hypotension despite adequate fluid resuscitation, with vasopressors targeting an initial goal MAP ≥ 65 mm Hg². Higher goals may be beneficial in patients with hypertension or atherosclerosis, which are common comorbidities in older patients. One study demonstrated that a target MAP of 80–85 mm Hg resulted in improved renal function when compared to standard targets in patients with a history of arterial hypertension³⁹. However, no differences in mortality were seen, and patients in the high target group had a greater incidence of atrial fibrillation. Individualized assessments of regional and global perfusion, such as lactate concentration, mental status, and urine output are also important monitoring and treatment targets.

Vasoactive agents are broadly differentiated into (1) vasopressors, (2) inotropes, or (3) vasodilators. Agents commonly have several of these properties and are largely effective in establishing minimally acceptable MAP to maintain organ perfusion. The receptor pharmacology of each vasoactive agent ultimately determines the physiologic properties and impact on various hemodynamic parameters in terms of both important beneficial and adverse effects. The selection of a specific agent is largely guided by balancing the beneficial hemodynamic effects and unwanted adverse effects. Safety concerns may be amplified in older adults, particularly those with multiple co-morbid disease states. SSC guidelines support norepinephrine (NE) as the preferred vasopressor, particularly when

hypovolemia is not yet resolved and IV fluid administration is ongoing². However, the choice of vasopressor in septic shock remains a matter of debate even after the latest guideline publication⁴⁰.

Vasopressors work primarily by augmenting systemic vascular resistance and some agents also increase cardiac output (CO). For example, NE is a potent alpha-1 and beta-1 adrenergic agonist. Dopamine (DA) has both alpha- and beta-adrenergic activity as well, but at different degrees than NE and has additional activity at dopaminergic receptors. Alpha-adrenergic mechanisms improve MAP by increasing vascular tone but may decrease CO and regional blood flow in cutaneous, splanchnic, and renal tissues. Beta-adrenergic mechanisms maintain blood flow through inotropic and chronotropic effects and increase splanchnic perfusion. However, they can also have unwanted consequences such as tachycardia, increases in cellular metabolism and immunosuppressive effects. Tachycardia affects the myocardium by reducing myocardial oxygenation and perfusion and increasing myocardial oxygen demand. In previous studies, a high heart rate was associated with increased mortality in septic shock^{41–43}.

Because of their similarities, several clinical trials have compared NE and DA in patients with septic shock. Compared to NE, DA demonstrates a higher relative risk of short-term mortality, tachycardia, and new diagnosis of arrhythmia^{44,45}. Based on these trials, the routine use of DA is not supported and is only recommended as an alternative vasopressor agent to NE in select patients such as those with low risk of tachyarrhythmias and absolute or relative bradycardia. DA is the only agent that can be administered through peripheral access and is a reasonable option in the early care of patients who do not yet have an established central line access. Use of DA at low doses, for dopaminergic effects, has no impact on patient outcomes and its use in this role should be discouraged⁴⁶.

Epinephrine is recommended as the alternative vasopressor added to and potentially substituted for NE when an additional agent is needed to maintain adequate blood pressure. Epinephrine has more potent effects on alpha- and beta-adrenergic receptors than NE and DA, and also stimulates beta-2 receptors. These added effects may have a deleterious impact on lactate clearance and splanchnic circulation, though this has not translated into worse outcomes in clinical studies⁴⁷. Studies comparing epinephrine and NE found no difference in mortality or adverse effects including tachycardia and arrhythmias².

Phenylephrine is a pure alpha-adrenergic agonist. It does not pose a risk of tachycardia due to its potent vasoconstrictor effects, but the high probability of decreasing stroke volume places this agent as a last-line vasopressor. In the treatment of septic shock, phenylephrine is not recommended except in cases of NE-associated arrhythmias, high CO states, or as salvage therapy when other vasopressor agents have failed⁴⁸.

Vasopressin is an adjunct to catecholamines in patients with severe septic shock based on the relative vasopressin deficiency hypothesis: endogenous vasopressin levels are relatively lower than anticipated in the majority of patients between 24 and 48 hours as shock continues, and administering exogenous vasopressin will restore vascular tone and blood pressure, thereby reducing the need for catecholamines. Vasopressin replacement therapy

increases overall blood pressure but has unclear effects on blood flow to local areas such as the heart, kidneys and intestine. Higher doses of vasopressin (>0.05 units/min) are associated with cardiac arrest and digital and splanchnic ischemia⁴⁹. The addition of 0.03 units/min of vasopressin to NE resulted in no difference in mortality compared to NE alone in patients with septic shock. However, vasopressin did demonstrate a mortality benefit and “catecholamine-sparing” effect in patients with less severe shock^{2,50}. Current SSC guidelines recommend vasopressin 0.03–0.04 units/min as add-on therapy to NE to achieve target MAP or to decrease NE dosage requirements. Vasopressin monotherapy is not recommended and higher doses should be avoided².

Maintaining high CO in sepsis is generally associated with a better outcome and is one of the important targets of EGDT⁵¹. However, the use of inotropic drugs to boost CO and oxygen delivery in established septic shock has been shown to lead to an increased mortality rate. Septic shock patients who remain hypotensive after adequate IV fluid resuscitation may have low, normal, or increased CO. As a result, treatment with a combined inotrope/vasopressor, such as NE or epinephrine, is recommended if CO is not measured.

When CO can be measured, a vasopressor, such as NE, may be used separately to target specific levels of MAP and CO. The first choice inotrope for patients with measured or suspected low CO in the presence of adequate fluid resuscitation and MAP is dobutamine. The SSC guidelines recommend a trial of dobutamine in situations of myocardial dysfunction or ongoing tissue hypoperfusion despite adequate intravascular volume and MAP. Use of a strategy to increase cardiac index to predetermined supranormal levels has not been found to be beneficial and should be avoided^{2,52}.

Recently the main focus of clinical trials, since the last SSC Guideline update, has been to evaluate the use of EGDT to provide fluid resuscitation in all septic patients. The main use of vasopressors, in addition to IV fluids, is to achieve a MAP ≥ 65 mm Hg, but there are many controversies on addition of vasopressors, including the type of vasopressor to achieve MAP goals. Questions remain about targeting a higher MAP goal (80–85 mm Hg) may be beneficial in older adults due to additional comorbidities, but clinical trials nor the SSC support this goal elevation. Although many clinical trials include the older adult population, there are not subgroup analyses or specific recommendations for clinicians to extrapolate to older adults for fluid resuscitation at this time.

Antibiotics and Source Control

The SSC 2012 Guidelines strongly recommend that an appropriate broad-spectrum antibiotic regimen be administered within one hour of recognition of severe sepsis or septic shock². As previously mentioned, timely recognition of sepsis is challenging in older patients. Patients with atypical symptoms, such as a general decline in health status, inability to perform activities of daily living, change in mental status, or incontinence, are more likely to have increased mortality rates from sepsis. In order to improve recognition of sepsis and timely administration of antibiotics, patients with atypical symptoms should be evaluated for possible sepsis and treated aggressively.

Proper selection and dosing of antimicrobial regimens are also critical. Inappropriate empiric therapy is an independent predictor of mortality, particularly in older adults⁵³. Antimicrobial regimens should include one or more agents that have activity against all likely pathogens². Several factors should be taken into consideration when selecting agents, including suspected site of infection, co-morbidities, antibiotic exposure in the past 30 days, and nursing home residence. If available, a patient's prior culture results and facility-specific antibacterial surveillance data can also be helpful. Older adults are approximately 1.3 times more likely to have gram-negative pathogens when compared to younger age groups^{23,54}. Multi-drug resistant organisms, such as methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant Enterococci, and extended-spectrum Beta lactamase-producing organisms are also more likely to be identified in residents of long-term care facilities³⁴. Based on the site of infection in older adults, there are slight differences in pathogens that require broad spectrum antibiotics (Table 2). Broad-spectrum antibiotics should be started initially and then de-escalated as appropriate². Antibiotics should always be started at full initial doses and then adjusted based on renal function².

Once a regimen has been selected, it is important to monitor for potential adverse drug reactions (ADR) in older adults, as ADRs occur 2–3 times more often in this population⁷. This is especially important to note in patients with sepsis, as antimicrobials have been shown to be among the most common therapeutic classes associated with ADRs in the geriatric population. For example, aminoglycosides (ie. tobramycin) have been shown to have an increased incidence of ototoxicity in older adults; however, this may be in part due to inappropriate dosing in patients who tend to have impaired baseline renal function. Fluoroquinolones are another class that poses a particular risk to older adults, as these patients tend to have longer QT intervals, making them at a higher risk for dangerous fluoroquinolone-induced QT prolongation.

Source control is also important in septic, older adults. Guidelines advocate for rapid identification of infection and source control intervention within 12 hours². The most common infection sites in older adults with severe sepsis include lungs, urinary tract, and abdomen⁵⁴. Source control procedures include removal of catheters, drainage of abscesses, debridement of necrotic tissue, and removal of empyema. Conservative management approaches that do not address source control should be avoided.

Supportive Care

Patients with severe sepsis, regardless of age, require a considerable number of supportive care interventions². Ventilated patients should receive protocol-based sedation with daily interruption for assessment and spontaneous breathing trials as tolerated⁵⁵. Older adults are at high risk of ICU delirium, and it is particularly problematic in those with underlying dementia⁵⁶. Preventative strategies are paramount, including routine delirium assessments, adequate pain control, prevention of constipation, and avoidance of deliriogenic medications such as benzodiazepines and anticholinergic agents⁵⁵.

All patients should receive venous thromboembolism prophylaxis with low molecular weight- or unfractionated heparin unless contraindicated and stress ulcer prophylaxis with a proton pump inhibitor or histamine-2 receptor blocker². Patients should receive protocol-

based glucose management targeting blood glucose < 180 mg/dL and avoidance of hypoglycemia. Enteral nutrition should be initiated in the first 48 hours of care if feasible. This is particularly important in older adults, as they may not have adequate nutritional status prior to admission.

End of Life Care

Setting goals of care and end of life planning are important concepts for septic, older adults, and are areas that are often overlooked. The SSC guidelines provide recommendations regarding goals of care that are paramount to all sepsis patients, but are especially important for the older adult population: goals of care and prognosis should be 1) discussed with patients and families, 2) incorporated into treatment and end of life care planning, and 3) discussed as soon as feasible, but no later than 72 hours after ICU admission⁵⁷.

Any discussion of end of life planning should focus on two key concepts: ethical decision making and shared decision making. The four ethical principles are autonomy (self-determination), beneficence (do good), non-maleficence (do no harm), and justice (equal treatment and equal access to treatment)⁵⁷. In addition to these, many believe that veracity should also be included – that one cannot exercise autonomy without being told all that they need to make an informed decision⁵⁸.

Shared decision making is the approach that allows patients, families, and clinicians to share in the care process, with an understanding that not everyone desires or is comfortable with the same approach. The shared decision making continuum allows for a balance between these two concepts, as long as communication and judgment between all parties is optimal⁵⁹. In order to achieve this, several variables must be taken in account and shared between everyone involved in the patient's care. These include a full understanding of the patient's medical condition and prognosis, their future quality of life, the organization of care, the attitudes of the medical staff, and their cultural and religious beliefs⁶⁰.

An eleven-year review of severe sepsis trends in the United States showed a dramatic increase in the rates of both hospitalization and fatalities in the population over 65 years of age over time, and especially compared to those under 65 years of age⁶¹. Due to the increasing severity and mortality associated with sepsis in older adults, it is reasonable to consider that there are limits to the aggressive treatment courses in the ICU and that limitations or withdrawal of care may not only be in the patient's best interests, but may be their legal right. While the full involvement of patients and their families in the treatment process is progressing, there is room for improvement by implementing strategies that integrating everyone involved into the patient care rounding process, providing daily reviews of treatment care plans, and early involvement of palliative care services.

Expert Commentary

Diagnosing and managing sepsis in older adults is challenging due to atypical symptom presentation. Temperature response is blunted and delayed in older adults due to poor peripheral thermal regulation and decreased cytokine production. Clinicians can identify shaking chills and an elevated temperature during a physical exam as good predictors of

bacteremia in older adults. Although, there are not specific temperature recommendations in older adults, clinicians should continue to assess any change from the patient's baseline instead of relying on designated, absolute temperature values. Older adults have multiple factors including immunosenescence and age-related changes, including skin breakdown and decrease of coughing reflex, which increase their risk of infection.

There are recommendations when providing treatment for older adults with sepsis. If an older adult requires fluid resuscitation due to septic shock, it is important to provide a fluid challenge of 30 mL/kg IV followed by continuous fluid therapy. However, it is important to avoid excessive resuscitation as it may cause additional harm to older adults with heart failure or significant renal impairment. If the older adult is exhibiting life-threatening hypotension, the addition of vasoactive agents is recommended to achieve of MAP 65 mm Hg to maintain perfusion. There are studies that suggest targeting higher MAP (80–85 mm Hg) for patients with atherosclerosis and hypertension; however, none of these studies demonstrated change in overall mortality. Appropriate broad spectrum antibiotics (covering both gram-positive and gram-negative organisms) should be initiated within the first hour of sepsis diagnosis since older adults are at an increased risk of contracting *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus*, and pathogens that are resistant to more narrow-spectrum antibiotics. Common antibiotics used for the treatment of sepsis (ie. vancomycin, piperacillin-tazobactam, meropenem, tobramycin) require dosage adjustment due to renal insufficiency, which may increase risk of potential adverse drug reactions (ie. nephrotoxicity, ototoxicity, seizures, etc.).

Five-Year Review

As the adult population continues to age into the older adult population, their risk for infection will continue to increase. There are a lack of studies and clinical trials evaluating the treatment of older adults with sepsis. There needs to be additional studies to evaluate special populations that are commonly affected by sepsis, including older adults.

In conclusion, sepsis is a time-dependent syndrome, and late diagnosis can lead to increased mortality risk if not diagnosed and treated appropriately. Older adults that contract sepsis have greater mortality risks due to delay in time to diagnosis. There are areas that need additional research in this special population as well as recognition of specific guidelines within future updates of the Society of Critical Care Medicine's SSC guidelines. With the aforementioned recommendations, clinicians should be able to apply the recommendations to identify and diagnose sepsis in older adults who present with atypical symptoms and provide appropriate treatment to optimize outcomes.

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“* of interest”

“** of considerable interest”

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Key Issues

- Immunosenescence, additional comorbidities (including diabetes and chronic kidney disease), and inflammaging lead to increased risk of infection in older adults
- Sepsis can be more difficult to diagnose in older adults, who tend to present with atypical symptoms and lack some of the classic SIRS criteria, especially temperature $\geq 38^{\circ}\text{C}$
- Drug selection can be challenging in this patient population due to multiple pharmacokinetic and pharmacodynamics changes related to aging
- Older adults are at increased risk of contracting drug-resistant pathogens and additional gram-negative bacteria; therefore, broad-spectrum antibiotics should be dosed appropriately during initial doses, but then may need to adjust doses based on renal function especially in older adults.
- Vasopressors may be needed in order to help achieve appropriate MAP levels; however, appropriate MAP levels in older adults have not been specified, nor have the appropriate vasopressors for older adults been identified
- Fluid resuscitation is needed for all patients who are hypotensive with a sepsis diagnosis to achieve a MAP $\geq 65\text{ mm Hg}$
- Older adults are at higher risk of developing ICU delirium and clinicians need to perform routine delirium assessments, adequate pain control, prevention of constipation, and avoidance of benzodiazepines, anticholinergic agents, and other deliriogenic medications
- As mortality increases with delayed sepsis diagnosis, clinicians should discuss goals of care and prognosis with patients and families; incorporate those goals into treatment and end of life care planning; and discussed when feasible, but no later than 72 hours after ICU admission.

Table 1

Risk Factors for Infections/Sepsis/Increased Mortality in Older Adults

Severe Infection	Severe Sepsis and Increased Mortality
Skin Breakdown, Cognitive Impairment	Medical comorbidities
Cough reflex diminished	Reduced cardiopulmonary reserve
Decreases in circulating thyroid hormone and endogenous corticosteroids	Age-related organ decline
Immunosenescence	Intact innate immune responses and cytokine production
Malnutrition	

Table 2

Site Specific Pathogens for Older Adults

Site	Pathogens
Urinary Tract	<i>Escherichia coli</i> <i>Proteus mirabilis</i> <i>Klebsiella species</i> <i>Enterobacter species</i>
Lung (Non-aspiration Pneumonias)	<i>Streptococcus pneumonia</i> <i>Enterobacteriaceae</i> <i>Staphylococcus aureus</i> <i>Pseudomonas aeruginosa</i>
Lung (Aspiration Pneumonias)	<i>Peptostreptococcus spp.</i> <i>Fusobacterium spp.</i> <i>Prevotella spp.</i> <i>Streptococcus pneumonia</i> <i>Staphylococcus aureus</i>
Skin and Soft Tissue	<i>Streptococcus spp.</i> <i>Staphylococcus spp.</i> <i>Pseudomonas aeruginosa (diabetic foot infections)</i>