Sepsis in Older Patients: An Emerging Concern in Critical Care

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Severe sepsis is a common problem associated with substantial mortality and a significant consumption of healthcare resources. The number of cases per year, currently estimated at 750,000 in the US alone, is expected to increase at a rate of 1.5% per year, and an increasingly significant proportion of these patients will be elderly. Older persons are more prone to infections due to the effects of aging, comorbidities, use of invasive devices, and problems associated with institutionalization. The diagnosis of sepsis in this population can be difficult, as older patients may have atypical responses to sepsis and may present with delirium or falls, thus delaying therapeutic interventions that may influence their outcome. There is a tendency to treat older persons less aggressively; however, it is important to consider criteria other than just chronological age, such as recent performance level, quality of life, comorbidities, and patient preference, when determining the aggressiveness of care. Future studies should focus on both short- and long-term outcomes of older patients, such as their ability to achieve previous physiological status and social independence, in addition to their risk of mortality after an event of severe sepsis.

Severe sepsis is a very common and important cause of morbidity and mortality in the older population, and its incidence has increased in the last 10 years [1]. It is estimated that about 750,000 patients per year develop severe sepsis in the US, of which nearly 60% are >65 years-of-age [2,3]. This is also reflected in the changing demographics of intensive care units (ICUs), where nearly two-thirds of beds are occupied by those >65 years old [3]. Aging patients account for 40–50% of all cases of bacteremia, and the overall case fatality rate for older patients with bacteremia ranges from 40–60%, or higher when Gram-negative organisms are involved [4,5,6]. This segment of the population will increase significantly over the coming years, driving an increase in the amount of resources used on these patients, who are thought to have a shortened life span [7].

This review analyzes the characteristics of older patients, discusses the unique aspects of severe sepsis in this increasingly important segment of our society, and provides a better understanding of the special needs of these patients. We also outline areas of future research that might improve outcomes in this patient population.

Methods
We performed a Medline search of the literature from 1996 to September 2001, using the keywords ‘sepsis’, ‘aged’, and ‘elderly’ and limiting the search to human studies and English language publications. The search identified 3159 articles, which were reviewed initially by title, followed by abstract to determine their relevance for inclusion. A total of 57 articles were reviewed in depth to determine the methodological rigor and content, of which 42 articles were retained for inclusion in this report.
Clinical Case
A 90-year-old retired physician presented to the emergency department with a 1-day history of shortness of breath and cough. He denied chills or fever, but had marked mental status changes that had begun approximately 36 h earlier. On examination his vital signs showed:

- blood pressure of 98/65 mmHg
- heart rate of 70 beats/min (paced)
- respiratory rate of 32 breaths/min
- temperature of 36.7°C.

The patient had rhonchi at the right lung base, anteriorly and posteriorly, with no dullness to percussion. His white blood cell count (WBCC) was 11 800 cells/µL, and his renal function showed a blood urea nitrogen (BUN) level of 28 mg/dL and creatinine level of 1.6 mg/dL. His admission chest X-ray is shown in Figure 1. The patient was begun on intravenous antibiotics, including ceftriaxone and levofloxacin, supplemental oxygen, and aggressive fluid resuscitation. Despite these interventions, his condition deteriorated requiring increased oxygen support, his WBCC rose to 23 000 cells/µL, and his BUN and creatinine levels increased to 42 mg/dL and 2.6 mg/dL, respectively. His chest X-ray at 72 h is shown in Figure 2. All the patient’s cultures remained negative, and he completed a 14-day course of intravenous antibiotics. The patient eventually recovered and was discharged home following a lengthy stay of 31 days.

As illustrated in this example, older persons often do not present with the classical signs and symptoms of systemic inflammatory response. Despite sepsis-induced organ dysfunction, this patient initially had only one of the classically defined systemic inflammatory response syndrome criteria — tachypnea. He had no fever, and had not mounted a tachycardic response, probably because of his pre-existing cardiac conduction disease. He also demonstrated a delayed rise in his WBCC. Clinicians might be misled by such a presentation, causing a delay in disease recognition and perhaps jeopardizing the timely administration of appropriate therapies and, therefore, the patients’ ultimate outcome. In addition, clinicians may be less inclined to treat older persons aggressively based solely on their age — a decision that may be inappropriate for a substantial number of older patients with a minimal burden of comorbidity and a good premorbid state of health and quality of life.
Epidemiology of severe sepsis

Due to the varying clinical manifestations of severe sepsis, and the vagaries of physicians’ chart documentation and death certificate practices, accurate estimates of the incidence of severe sepsis have been difficult to establish. This is particularly evident in the variability that exists between different studies, with incidence estimates from past studies ranging from 73.6 per 100,000 populations, to 175.9 per 100,000 populations [1,8].

The recent observational cohort study conducted by Angus et al. [2] reported on the incidence of severe sepsis in seven US state hospitals, using criteria based on the International Classification of Diseases, 9th Revision, Clinical Modification codes, rather than the 1992 American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) guideline definitions [9]; i.e. sepsis associated with acute organ dysfunction. The estimated incidence of severe sepsis in this study was three cases per 1000 population. Astoundingly, the age-specific incidence of severe sepsis increased 100-fold to 26.2 cases per 1000 population in older patients. Mortality also steadily increased as patients aged, with a peak of 38.4% in patients >85 years [2,3] (Fig. 3).

Many ICU patients with either preexisting infections at ICU admission, or who develop nosocomial infections in ICU, go on to develop sepsis. A recent international prospective cohort study demonstrated a 21.1% crude incidence rate of infections in ICU patients [10]. About 28% of infections were associated with sepsis, 24% with severe sepsis, 30% with septic shock, and 18% were not classified.

In a second prospective cohort study, Rangel-Frausto et al. defined the epidemiology of patients with two, three, or four systemic inflammatory response syndrome (SIRS) criteria, sepsis, severe sepsis, and septic shock [11]. Of the 3708 patients admitted to the survey units, 2527 (68%) met the criteria for SIRS. Among patients with SIRS, 649 (26%) developed sepsis, 467 (18%) developed severe sepsis, and 110 (4%) developed septic shock. There was a stepwise increase in mortality rates in the hierarchy from SIRS, sepsis, severe sepsis, and septic shock: 7%, 16%, 20%, and 46%, respectively. Of interest was that the investigators observed equal numbers of patients who appeared to have sepsis, severe sepsis, or septic shock, but had negative cultures. This indicated that the outcome of sepsis was related to the severity, reflected in the age-specific incidence of severe sepsis.
by the degree of organ dysfunction, and not the presence of bacteremia.

Sepsis, along with the frequent comorbid conditions of acute lung injury necessitating mechanical ventilation, is a major public health concern in older patients. Severe sepsis consumes considerable healthcare resources, with an estimated annual cost of $16.7 billion in the US in the year 2000 [2,3]. The appropriateness of spending these resources on older patients with this life-threatening illness is a point of continued debate.

Pathophysiology
Infection is the most common causes of sepsis, however, in many sepsis patients the infectious etiology is not identified. The same biochemical and physiological changes as those seen with infectious agents may also present in other non-infectious conditions, such as pancreatitis, trauma, or extensive burns. It was once thought that the response to the initial insult or triggers precipitated a cascade of events where interleukin-1 (IL-1), IL-6, and tumor necrosis factor (TNF) played a central role [6,11,12]. With our current greater understanding of the inflammatory cascade, we now know that sepsis is caused by an imbalance in the normal inflammation and coagulation responses of the patient.

On the one hand, cytokines IL-1, IL-6, and TNF-α alter the secretion of hormones, which in turn direct an increase in the resting energy expenditure: amino acids are exported from the muscles to the liver, gluconeogenesis increases, and a catabolic state is created. On the other hand, these cytokines cause increased neutrophil activation, and directly damage organs by activating the coagulation cascade and inhibiting fibrinolysis [13]. This leads to diffuse endovascular injury, and can lead to multiorgan dysfunction and death [6].

Risk factors for the older patient
Aging is a process associated with numerous risk factors that contribute to the increasing incidence of, and mortality from, severe sepsis.

Performance status
A number of aging processes lead to poorer performance status, an independent predictor of mortality [13–15]:

- disuse atrophy from an inactive life-style
- sarcopenia from accelerated muscle loss
- changes in responsiveness to trophic hormones (growth hormones, androgens, and estrogens)
- neurological alterations
- altered cytokine regulation
- changes in protein metabolism
- changes to dietary intake.

Immune function
Older patients are often nutritionally or immunologically impaired [16], making them an easy target for infection and its associated complications. They are frequently affected by comorbidities that require treatment with foreign devices (e.g. indwelling urinary catheters, gastrostomies, cystostomies, tracheostomies, peripherally inserted catheters) that make patients vulnerable to infections or complications. The natural barriers of innate immunity are broken, providing increased access for pathogens [13,17,18]. There is also evidence of abnormal T and B cell function in older patients [16], although the response to infection appears to elicit a normal expression of proinflammatory cytokines [19].

Nutrition
One of the physiological changes of aging includes a substantial decrease in olfactory discrimination by age 70; sweet, sour, bitter, and salty tastes are impaired [13], which contributes to a decreased enjoyment of meals, aggravating the anorexia of aging. An older patient's nutritional status can also be affected by [13]:

- inactivity
- inadequate funds or resources
- mobility and transportation issues
- social isolation
- functional limitations
- poor or restricted diets
- chronic disease
- dementia
- depression
- poor dentition
- polypharmacy
- alcohol or substance abuse.

Drugs
The medical community is in need of an improved understanding of how drug absorption, hepatic metabolism, and drug responses vary with old age. It is evident that drug clearance from the body, particularly through renal mechanisms, is altered in aging persons [18]. Age-related decline in renal function predominately underlies the decreased drug clearance. Because the kidneys are largely responsible for the excretion of several antibiotics, dose adjustments and monitoring of serum drug levels may be necessary for certain drugs in older patients. Testing only blood creatinine levels could
underestimate or overestimate the renal function of these patients, and therefore creatinine clearance would be a better assessment of their kidneys' functional capacity.

Certain antibiotics are associated with increased side effects in older patients (Table 1) [18]. Drug interactions are also increased in the elderly; however, this is as a consequence of the greater number of medications taken, rather than age.

Social changes
Institutionalization (e.g. nursing homes) is common amongst older people, who have to go through a period of adjustment to their new environments. Adequate social support should help them through the process easily, and minimize the associated problems, such as depression, crowding, and neglect, all of which have impact on nutrition and immunity.

Clinical manifestations of sepsis in the older patient
The septic process is characterized by a series of signs and symptoms that include:

- fever or hypothermia
- leukocytosis or leukopenia
- tachycardia
- tachypnea.

This SIRS, if not recognized early and treated aggressively, can progress to a cascade of events that leads to the development of diffuse endovascular injury, microvascular thrombosis, organ ischemia, and death [3,5,6,11,12,20].

Older patients pose particular challenges in the diagnosis and early management of sepsis. Firstly, obtaining diagnostic specimens that require patient cooperation in the frail, debilitated, cognitively impaired, or severely ill elderly patient can be challenging.

More importantly, the classical manifestations of the SIRS may be minimally present, as illustrated in the clinical case above. Healthcare professionals who are not astute in recognizing these variations may delay important interventions that will affect the final outcome of these patients.

Clinical manifestations of infections in older patients may be unusual, nonspecific, or absent, and can include weakness, malaise, delirium, confusion, loss of appetite, falls, or urinary incontinence [18]. Fever, a hallmark of infection, can also be blunted or absent in infected older patients. Although body temperature elevations in elderly persons are an indicator for the presence of serious infections, decreased body temperature (hypothermia) is a more ominous sign.

The common sites of infection in the elderly are similar to patients of other age groups, involving the respiratory, urinary, and gastrointestinal systems, and the skin and soft tissues [12]. The organisms found most frequently are Gram-negative bacilli, but there has been a rapid increase in the incidence of Gram-positive cocci infection [1]. This increase in prevalence is probably due to the institutionalization of aged patients, and an increased early use of broad spectrum antibiotics, which selects for more virulent and resistant strains.

Therapeutic options
The septic process can be altered or modified if it is recognized early, and adequate supportive care is promptly initiated. The most important intervention is to make a rapid diagnosis — a difficult task to achieve given the atypical presentation of sepsis in the older patient. Once the diagnosis has been made, appropriate antibiotics must be administered in an attempt to halt the triggers for the continued inflammatory cascade. Survival can be compromised significantly if there is a delay in the use of the antibiotics, as demonstrated in several studies [21,22].

Recent advances in the understanding of the septic process have helped to develop new therapeutic options, and research is promising other therapeutic options in the coming years. Several potential targets for intervention in the inflammatory cascade have been identified, including:

- TNF [23,24]
- endotoxin [25]
- IL-1 [26–28] and IL-6 [29]
- phospholipase A₂ (a current ongoing trial)
- antithrombin III (AT III) [30]
- platelet-activating factor (PAF) [31]
- tissue factor pathway inhibitor (unpublished data)
- Activated Protein C [6].

**Table 1. Antibiotics associated with increased side effects in older patients.**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Side effect</th>
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<td>Aminoglycosides</td>
<td>Renal dysfunction</td>
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<td>Auditory nerve dysfunction</td>
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<td>β-lactams</td>
<td>Seizures</td>
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<td>Skin rash</td>
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<td>Macrolides</td>
<td>Nausea</td>
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<td>Abdominal cramps</td>
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<td>Quinolones</td>
<td>Seizures</td>
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<td>Hallucinations</td>
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<td>Vancomycin</td>
<td>Renal dysfunction</td>
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The clinical trials of monoclonal anti-endotoxin antibody and AT III replacement therapy were unable to show a significant short-term survival improvement [20–22,29]. From these and other agents currently being studied, we hope to find interventions that will reduce the mortality of both acute respiratory distress syndrome (ARDS) and sepsis. For example, while clinical trials with PAF receptor antagonists failed to show short-term survival advantage, in a recent study designed to prevent the development of ARDS using recombinant PAF-acetylhydrolase within 12 h of the onset of sepsis or trauma, there was a significantly reduced mortality in the subgroup analyses of patients with severe sepsis [32]. These results are being validated in a large, Phase III, multicenter trial.

Steroids, ibuprofen, and other drugs have also been used in an attempt to halt the inflammatory response, with an overall paucity of clinically-meaningful positive results [33,34]. Abnormalities in adrenal cortisol production predict a very high mortality rate in sepsis [35], and a recent study documents that low-dose steroids might be of benefit in some cases of refractory sepsis [36].

In March 2001, Bernard et al. [6] reported on the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial of drotrecogin alfa (activated) — the official generic nomenclature for human recombinant Activated Protein C — in severe sepsis. They identified a 6% absolute risk reduction (19.4% relative risk reduction) in the 28-day mortality of the study group compared with the placebo group. On subgroup analysis, drotrecogin alfa (activated) appeared at least as effective for patients >65 years old as it was for younger patients, with no detectable increased risk of bleeding [37].

Adequate supportive care with close monitoring, adequate nutrition, ulcer and deep venous thrombosis prophylaxis, and ventilatory support should be considered essential components of the plan of care in any aged patient with sepsis. Some authors have suggested the use of antiseptic bonded central-line catheters to reduce the number of catheter-related sepsis cases, with some positive results [17].

Recent studies have documented that older patients are treated less aggressively than their younger counterparts [38,39], particularly those >85 years old [40], and that race further affects the level of care provided [41]. This may be due to the belief that the aged patients have a significantly shorter life span, are too weak to cope with the great physiological demands involved with surviving the septic process, and survivors are likely to become dependent, requiring social and economical support; by stepping up the care, pain and suffering will be unnecessarily increased. However, treatment decisions based solely on age without considering other prognostic factors (discussed below), could lead to a substantial number of older patients who could benefit from more aggressive treatment being under-treated.

Because new antisepsis therapies are likely to be expensive, a better understanding of both their clinical-effectiveness and cost-effectiveness in all patient groups is essential. Sepsis is a disease of the elderly, therefore it is important to consider appropriateness of care, including the determination of patient preferences. Unfortunately, clinical trials of antisepsis agents tend to exclude the very elderly, as they are believed to be less likely to respond to treatment. However, these patients form a large proportion of the sepsis population, and their exclusion compromises the validity of these trials and limits our understanding of treatment options for this group.

**Prognosis of severe sepsis in the older patient**

Severe sepsis is a common entity with bad prognosis across all age groups. Factors that have been used to predict outcomes in critically ill patients include [14,15]:

- pre-infectious immune or genetic status
- gender
- age
- nosocomial events
- comorbidities
- severity of illness.

Although population studies have shown that older people do have a higher mortality associated with severe sepsis, it is important that the clinician separate the general prognosis of a population of older patients from that of the individual. Chronological age alone should not be used either to predict the outcome or determine treatment options for individual patients. Although age is an important factor used to predict length of stay in the ICU, the increased mortality observed in older patients with severe sepsis is thought to be due to the increased comorbidities among this group [38], the most important of which are [2]:

- metastatic neoplasm (43.4%)
- chronic liver disease (37.1%)
- non-metastatic neoplasm (36.9%)
- chronic renal disease (36.7%)
- chronic obstructive pulmonary disease (32.1%).

Despite the fact that older patients tend to be less aggressively treated, aggressive care is not futile, and the majority of older patients survive until discharge.
Unfortunately information regarding subsequent survival and quality of life after an episode of severe sepsis is limited, especially in the elderly. We know, for example, that after an episode of respiratory failure, a patient has a significantly high risk of poor quality-adjusted survival [42]. Such data are crucial to determine optimal healthcare policies as the population ages and the number of cases of sepsis increases. We are unaware of any recent studies addressing this question, but they may be already underway.

Summary and conclusion
Sepsis is a frequently encountered problem, with substantial mortality and a significant consumption of healthcare resources, that predominantly affects older persons. It is estimated that the number of cases of severe sepsis will grow at a rate of 1.5% per year, as projected from the US 2000 census, so that by 2020 the number of cases will approximate 1 million per year [2], an increasingly significant proportion of which will be aged patients. This is expected to be a worldwide phenomenon.

Older patients are more likely to have comorbidities, problems associated with institutionalization, or have invasive devices, making them prone to infections. Older patients also pose a diagnostic dilemma; they show many atypical features of sepsis that make its early diagnosis and management difficult. Antibiotic therapy, adequate supportive care, and the use of newer interventions should play a part in the survival of these patients.

Although survival is the most important outcome, the quality of survival is also important. Given that the aggressiveness of therapy appears to be lower in older persons, despite representing a larger proportion of sufferers than any other age group, further studies will be important to justify or change current treatment regimes. Of particular importance are those studies looking at the short- and long-term ability of these patients to achieve previous physiological status, social independence, and quality of life, and their risk of mortality after an event of severe sepsis.

With the increase in the elderly population in coming years, understanding the extent of the problem, socially and economically, should help us to target therapeutic interventions in a more efficient and effective way.

References


39. Hall RI, Rocker GM. End-of-life care in the ICU: Treatments provided when life support was or was not withdrawn. *Chest* 2000;118:1424–30.

