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REVIEW

Severe sepsis and septic shock in the elderly: An overview

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Abstract

The incidence of severe sepsis and septic shock is increasing in the older population leading to increased admissions to the intensive care units (ICUs). The elderly are predisposed to sepsis due to co-existing co-morbidities, repeated and prolonged hospitalizations, reduced immunity, functional limitations and above all due to the effects of aging itself. A lower threshold and a higher index of suspicion is required to diagnose sepsis in this patient population because the initial clinical picture may be ambiguous, and aging increases the risk of a sudden deterioration in sepsis to severe sepsis and septic shock. Management is largely based on standard international guidelines with a few modifications. Age itself is an independent risk factor for death in patients with severe sepsis, however, many patients respond well to timely and appropriate interventions. The treatment should not be limited or deferred in elderly patients with severe sepsis only on the grounds of physician prejudice, but patient and family preferences should also be taken into account as the outcomes are not dismal. Future investigations in the management of sepsis should not only target good functional recovery but also ensure social independence and quality of life after ICU discharge.

INTRODUCTION

In recent years, the incidence of elderly patients being admitted to intensive care units (ICUs) has increased globally[1]. This process of "demographic transition" can be explained not only by a decrease in fertility, and hence birth rate, but also by a decline in mortality rates leading to increased life expectancy. It has been predicted that in the near future, the elderly will grow more rapidly than any other age group, and by 2050 the world's elderly population will exceed that of the young for the first time in history[2].

Sepsis is an important cause of morbidity and mortality in the older population. Studies on the diagnosis and management of sepsis usually exclude subjects with multiple co-morbidities or those in the very aged group (greater than 80 years); however, as the population becomes increasingly old and ill, this subset of the population will be admitted more frequently into the ICUs and their management will pose a serious challenge to the treating intensivists. Through this review, we have tried to analyze the susceptibility, risk factors, management and outcome of older patients with severe sepsis and septic shock. We have also tried to identify the areas for future investigations that might improve outcomes in this particular patient population.

EPIDEMIOLOGY

Sepsis is defined as an inflammatory body response to infection, with severe sepsis and septic shock being its more severe forms[3]. Despite advances in the management of septic patients, sepsis is still the second leading cause of death among patients in non-coronary ICUs[4]. The incidence and prevalence of sepsis increase with age[5]. Angus *et al*[5] studied discharge records for the year 1995 from 7 hospitals in the United States and found that the annual incidence of severe sepsis was 3.0 cases per 1000 population. However, the incidence of severe sepsis in older patients was 26.2 cases per 1000 population. The mean age of patients with severe sepsis was 63.8 years in this study, which increased to 68.2 years in the latter study[4,5]. The elderly constitute only one fifth of the US population, but they constitute two thirds of the patients admitted to hospital with sepsis[4]. The incidence of severe sepsis per se is also increasing[6,7]. Dombrovskiy *et al*[6] found a 1.7-fold increase in patients admitted with severe sepsis from 1993-2003. In another study by Martin *et al*[4], this increased incidence of sepsis was around 20% more in the elderly population as compared to younger patients. Similar findings of increased incidence of sepsis, with the mean age of patients with severe sepsis being around 60 years, have been reported in studies from the eastern part of the world[8,9]. Mortality rates associated with severe sepsis also increase with increasing age, with the highest mortality in old elderly (patients more than 85 years of age)[9-12]. There is a dearth of data regarding the outcome of elderly patients with sepsis and septic shock. A few studies which have been conducted in this specific patient population and have shown that severe sepsis and septic shock are common in elderly patients and these patients have an increased mortality as compared to their younger counterparts[4,6,9].

RISK FACTORS

There are various risk factors that predispose the elderly to an increased incidence of sepsis.

Preexisting co-morbidities and drugs for these chronic illnesses

The increased risk of sepsis in the elderly can be due to chronic co-morbidities such as cancer, diabetes, obesity, and human immunodeficiency virus, among others[6]. All of these are much more crucial in patients of advanced age. Previous comorbid illnesses like renal or pulmonary disease are commonly associated with increased susceptibility to sepsis[4,13,14]. However co-morbidities alone are not sufficient and other factors such as various drugs, instrumentation and recurrent hospitalization are also responsible for breaching an already compromised immunity[15].

Pre-admission functional status

Pre-admission functional status is much more important than comorbid illness and has been found to be an independent predictor of outcome in elderly patients[16,17]. There are numerous causes of poor functional status including[17,18]: (1) Disuse atrophy due to an inactive lifestyle; (2) Sarcopenia due to accelerated muscle loss; (3) Changes in responsiveness to trophic hormones (growth hormones, androgens, and estrogens); (4) Neurological alterations; (5) Altered cytokine regulation; (6) Changes in protein metabolism; and (7) Changes in dietary intake.

Malnutrition

Malnutrition is also common in the elderly and has been attributed to factors such as inactivity, inadequate funds or resources, mobility and transportation issues, social isolation, functional limitations, poor or restricted diets, chronic disease, dementia, depression, poor dentition, polypharmacy, and alcohol or substance abuse[18].

Endocrine deficiency

Elderly patients also have associated endocrine disorders like hypoadrenalism, hypothyroidism and hypogonadism which alter the response to sepsis, and hence, further predisposes them to increased risk of infection.

Aging

Several studies have found old age itself as an independent risk factor for predisposition to severe sepsis[4,19,20].

Other risk factors

The elderly are also at increased risk for colonization by gram-negative organisms, which may be multi-drug resistant, predisposing the elderly to sepsis[19]. The possible reasons for this increased colonization are nursing home residence, recurrent hospitalization and interventions such as urinary catheterizations, poor functional status or multiple drug use.

IMMUNE SYSTEM IN THE ELDERLY

The immune system in older age is abnormal and is in a state of immunosenescence[21]. The pathophysiology of this immunosenescence is complex and multifactorial. There are functional impairments in both cell-mediated immunity and humoral immune responses with age[21]. The thymus, a major organ involved in adaptive cell-mediated immunity, atrophies with age and by 60 years loses most of its activity causing a shift in the T-cell repertoire from naïve T-cells to memory T-cells[21,22]. In response to antigens, these memory cells have limited proliferative capacity, express fewer co-stimulatory molecules like CD40 ligand and CD28, and lead to reduced activation of mitogen-activated protein kinase[22]. B cell and plasma cell populations also gradually decrease with aging[23]. However, polyspecific, low affinity T-cell independent immunoglobulin levels increase with age[23]. Some of these immunoglobulins behave as autoantibodies[24]. Although antibodies against previously exposed antigens are retained, the elderly have a decreased ability

to produce specific opsonophagocytic antibodies against neoantigens[21].

Innate immunity is not spared from the effects of aging, and many functions of innate immunity are affected. Macrophages undergo significant functional alteration, there is reduced antigen processing and expression to T cells, reduced bactericidal activity and altered expression and function of toll like receptors[25]. Besides macrophages, others cells involved in innate immunity like neutrophils and natural killer cells are also impaired causing reduced recognition and destruction of infected cells in the aged[26].

IMPACT OF AGEING ON PATHOPHYSIOLOGY OF SEVERE SEPSIS

In addition to the state of immunosenescence that predisposes the elderly to an increased rate of sepsis, there are also alterations in the body's response to sepsis, hence, leading to the more severe presentation of infection.

Severe sepsis led activation of the coagulation cascade plays a vital role in the pathophysiology of sepsis[21]. An aging led increase in plasma levels of fibrinogen, factor Ⅶ, factor Ⅷ, factor Ⅸ, and other clotting factors which is further potentiated during sepsis explains the increased risk of thrombosis and thromboembolism seen in the elderly[21]. There is also an increased rate of the generation of plasminogen activator inhibitor type 1 in the aged, which contributes to poor clearance of fibrin from the circulation of elderly patients[21]. This combined impact of aging and sepsis on the coagulation cascade partially explains the higher short survival rates with drotrecogin α (activated) in the Protein C Worldwide Evaluation of Severe Sepsis (PROWESS) trial[12,27].

There is also an abnormal cytokine response in the elderly[21]. There is a shift from the production of type 1 cytokines [interleukin (IL)-2, tumor necrosis factor (TNF)-α] to type 2 cytokines (IL-4, IL-10)[28]. However, IL-1, IL-3, TNF, interferon-γ, IL-8, and IL-12 production is generally unaffected or increased in the elderly[21]. This predisposes the elderly to systemic infection by microbial pathogens and generally more prolonged proinflammatory responses as compared to younger patients. This also reflects the abnormal response of counter-regulatory cytokines like IL-10 in clearing microbial pathogens[21].

The concept of sepsis-associated myocardial depression is due to several factors including TNF, nitric oxide and probably other inflammatory cytokines like IL-1 and IL-6 which have a negative inotropic effect[29]. This can be further aggravated by aging, leading to a poorer outcome in elderly septic patients[30,31]. The elderly response to endotoxins is also more severe with more profound hypotension, excess epinephrine response, delayed recovery of blood pressure and more profound cytokine response as compared to younger subjects[32].

DIAGNOSIS OF SEPSIS IN THE ELDERLY

The clinical diagnosis of infection in the elderly is challenging and likely to be missed if not anticipated. The presentation of sepsis in the elderly may be more severe and different from that in younger patients[10]. The initial inflammatory response of infection which normally produces symptoms and signs of sepsis are blunted or may be absent in the elderly, while later presentation may be very severe with very rapid progression to septic shock[13,21,26]. It has been shown that the febrile response may be blunted in up to 47% of elderly septic patients[33]. However, nonspecific signs of sepsis like altered mental status, delirium, weakness, anorexia, malaise, falls, and urinary incontinence are common in the elderly[13]. Similar findings can be present in non-infectious diseases in the elderly making the diagnosis difficult[13]. In addition, due to age-related dementia, a clear history may not be available in many patients. Thus, a lower threshold and higher index of suspicion is required to diagnose sepsis in this population[13,34]. Besides the abnormal response to infection, there are challenges in taking adequate diagnostic specimens in elderly patients because of a lack of cooperation in the frail, dehydrated, debilitated, and cognitively impaired[13,34]. Positioning of these patients due to osteoarthritis or other orthopedic problems may prove challenging when performing high-quality imaging studies which may compromise the diagnostic value of these studies[34].

In elderly patients, the most common source of sepsis is respiratory tract followed by genitourinary infections[4]. It is possible that the elderly are at increased risk of infection with multidrug-resistant organisms. In a review of patients treated at hematology and oncology centers in the United States and Canada an increased rate of detection of isolates like methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococci* in the elderly was observed. The incidence of Klebsiella species with extended-spectrum β-lactamase phenotyes was also found to be highest among patients older than 65 years and younger than 14 years[35].

The explanation for this disproportionate increased rate of multi-resistant organisms in the elderly is greater exposure to the health care system and cumulative antibiotic exposure, although studies are still lacking in this area to verify these findings.

MANAGEMENT OF SEVERE SEPSIS AND SEPTIC SHOCK IN THE ELDERLY

The management of severe sepsis and septic shock in the elderly should be performed as per the International Surviving Sepsis Guidelines[36]. The sepsis resuscitation and management bundles should be started early and have been shown to improve survival with good compliance over different age groups[37,38]. The similar principles of management as used in young adults, including early source control, early goal-directed therapy, use of low tidal volume during mechanical ventilation, should be followed. There are, however, a few specific considerations which should be kept in mind while managing severe sepsis and septic shock in the elderly.

Resuscitation

Early goal-directed therapy remains the mainstay of the resuscitation bundle in the management of severe sepsis and septic shock in both young adults and elderly patients[39]. Studies have proven the effectiveness of early goal-directed therapy in adults when used in conjunction with other measures of the sepsis bundles in the management of elderly patients[40]. Various measures which can be taken to improve cardiac output in the elderly should focus on systolic function rather than heart rate as the heart rate response to sepsis is blunted in the elderly[41]. The systolic output of the heart is dependent on left ventricular preload as per Starling's law. Therefore, it is necessary to maintain adequate preload, whenever an aged patient needs to increase his cardiac output, such as during sepsis[26]. However, overzealous fluid administration can also be problematic in patients with aging-associated diastolic dysfunction[41]. Other therapies to improve tissue perfusion like dobutamine can also have variable effects due to relative resistance in the aged and can be arrhythymogenic, especially in patients with a history of coronary artery disease[42]. Blood transfusion triggers should be the same as in young adults with the threshold to transfuse packed red blood cells being kept at a hemoglobin of less than 7 g/dL and a target hemoglobin of 7-9 g/dL[43]. However, the threshold of 7 g/dL contradicts the early goal-directed resuscitation (first 6 h of resuscitation) protocol that targets a hematocrit of 30% in patients with low central venous oxygen saturation, and in patients with active coronary artery disease which may be common in the elderly[40,44]. Vasopressors like dopamine or norepinephrine can be used to maintain perfusion in the face of life-threatening hypotension, despite appropriate fluid challenges[36].

Source control and antibiotics

The dosing of antimicrobials should be based on age-related differences in pharmacokinetic and pharmacodynamic parameters such as decrements in renal function including glomerular filtration rate, tubular secretion, and renal blood flow; reduced lean body mass and increase body fat, and shock-induced reduction in hepatic blood flow[45,46]. There is also an increased incidence of antimicrobial-related adverse effects in the elderly[46,47]. However, the principle of initial bolus dose and overall aggressive dosing to achieve maximal therapeutic dose should not be sacrificed to avoid potential adverse effects[46].

Source control of infection and early appropriate antimicrobials are the two vital components of the management bundle of surviving sepsis guidelines[36,37]. The source of infection should be identified without delay when possible, and appropriate source control measures like removal of infected foreign bodies (intravascular catheters), drainage of abscesses or other infected fluid collections, or definitive management of anatomical derangements sustaining microbial contamination should be contemplated early whenever possible[26,36].

The concept of inadequate initial antibiotic therapy is independently associated with poor outcomes and is valid across all ages[47,48]. The early institution of antimicrobial therapy has been found to significantly decrease mortality even in elderly sepsis patients[47-51]. Broad spectrum empirical antibiotic therapy should be initiated within 1 h of the recognition of sepsis, after samples of blood and other suspected sites of infection have been obtained for culture[36]. The empirical antimicrobial regimens should be based on patient-factors such as underlying co-morbidities or immune-compromised states, site and severity of infection; environmental factors such as residence in nursing homes, history of repeated hospitalizations and local factors like the expected microbiological organism and the antimicrobial susceptibility patterns[45,46]. The strategies of clinical response and culture-based de-escalation and shorter courses of therapy should also be used when appropriate[46].

Corticosteroids

Adrenal insufficiency is common among elderly patients with septic shock[52]. However, the laboratory findings of hyponatremia, hyperkalemia and eosinophilia, which may indicate the presence of adrenal insufficiency, are uncommon in these patients[52,53]. The use of steroids for septic shock has remained a source of controversy because of concerns regarding effectiveness of steroids per se, and on other hand, due to the serious adverse effects of steroids like hyperglycemia, immunosuppression (at high doses), poor wound healing, and exacerbation of myoneuropathy due to critical illness[54,55]. Adding to the controversy, Salgado *et al*[53] showed that advanced age may not be an independent risk factor for relative adrenal insufficiency. Hence, at present, due to lack of definitive evidence, we recommend that low dose intravenous hydrocortisone can be tried in elderly septic shock patients only in such clinical situations where the blood pressure is poorly responsive to fluid resuscitation and vasopressor therapy as recommended by the surviving sepsis guidelines[36].

Activated protein C (Drotrecogin α)

The PROWESS trial in 2001 showed a 6% absolute risk reduction (19.4% relative risk reduction) in the 28-d mortality in patients treated with recombinant human activated protein C (rhAPC) as compared to those who were given placebo[27]. Out of the 850 patients who were randomized in this study to receive rhAPC, 48.6% were more than 65 years of age and 24.1% were more than 75 years of age[27]. On subgroup analysis, in patients more than 75 years (386 patients), there was a 15.5% reduction in the absolute risk of mortality at 28 d and a 15.6% reduction in-hospital mortality in the treatment group as compared to the placebo group, with no detectable increased risk of bleeding[12]. Even long-term survival was significantly higher in the treatment group ($P = 0.02$) among the elderly patient subgroup[12]. Hence, treatment with rhAPC can be safely considered in elderly patients

with septic shock who are at a high risk of death due to severe sepsis, regardless of their age, if there are no contraindications[13,36]. The criteria for giving rhAPC remains the same as in younger patients, which is, Acute Physiology and Chronic Health Evaluation Ⅱ ⩾ 25 and/or patients with septic shock requiring vasopressors despite fluid resuscitation, with sepsis-induced organ dysfunction of more than two organ systems[37].

Respiratory failure and mechanical ventilation

Patients with severe sepsis and septic shock often require mechanical ventilation. The need for mechanical ventilation in the elderly is independently associated with increased mortality[10,56,57]. In the landmark study by the acute respiratory distress syndrome (ARDS) Network, the investigators found an absolute risk reduction in mortality of 9% (40% *vs* 31%) with a relative risk reduction of 22% in the low tidal volume (6 mL/kg) group, when compared with the conventional tidal volume (12 mL/kg) group[58]. On subgroup analysis of the 173 patients aged more than 70 years, ventilation with low tidal volume resulted in an absolute risk reduction of 9.9% in mortality at 28 d[59]. Thus, a tidal volume of 6 mL/kg (predicted) body weight in patients with acute lung injury (ALI)/ARDS is recommended even in elderly patients[60]. In addition, the plateau pressures should be measured in patients with ALI/ARDS and the initial upper limit goal for plateau pressures should be less than 30 cm H_2O. The data regarding weaning in the older population after ARDS are sparse, and general recommendations for younger adults can be followed in the elderly such as using standardized protocols to evaluate patients for weaning and using spontaneous breathing trials[60,61].

Glycemic control

van den Berghe *et al*[62], demonstrated a significant reduction in morbidity and mortality with intensive blood glucose (BG) control of 80 and 110 mg/dL in a primarily surgical ICU patient population. However, the same investigators could not demonstrate reduced mortality with an identical protocol in medical ICU patients, and there was a 6-fold increased rate of hypoglycemia (BG < 40 mg/dL) in the intensive BG control group (18.7% *vs* 3.1%)[63]. The higher rates of severe hypoglycemia associated with intensive insulin therapy were also seen in other trials and in a meta-analysis, thus, any benefit derived from strict glycemic control is partially offset by the serious adverse events of hypoglycemia[63-67]. The surviving sepsis guidelines recommend the maintenance of BG level < 150 mg/dL with the continuous intravenous infusion of insulin and glucose in patients with severe sepsis following stabilization in the ICU[36]. The risk of hypoglycemia is particularly common in elderly septic patients, and therefore, the target of 150 mg/dL seems to be safe in such patients.

Other issues

The other issues concerning the care of elderly patients with severe sepsis may include the use of sedation and analgesia, prophylaxis for deep vein thrombosis, and stress ulcer prophylaxis which should be followed as for the younger adults[37]. The use of protocolized sedation regimes with daily interruption of sedation, to reduce the duration of mechanical ventilation, should be followed[68]. This may include sedative drugs administered as an intermittent bolus rather than by continuous infusion[68]. Low-dose unfractionated heparin, low-molecular-weight heparin, or mechanical prophylactic devices should be used for the prophylaxis of deep vein thrombosis, and H_2-receptor blockers or proton pump inhibitors should be used to prevent stress ulcers[36].

End of life issues

Besides aggressive care of patients with severe sepsis and septic shock, physicians should also be prepared and be equipped to provide quality end-of-life care in elderly patients who have a dismal prognosis. The probability of a decision regarding withholding or withdrawing life-sustaining treatments increases with patient age, however, such decisions should not be based on the futility of treatment, but should be individualized and centered around patient and family wishes[69-71]. This involves advance care planning, including the clear communication of likely outcomes and realistic goals of treatment to the family of the patient or the patient whenever possible. The final decision of limiting or withdrawing treatment may be followed as per the local guidelines. In difficult or more complex situations, the hospital ethical committee or the equivalent teams may provide assistance in decision-making regarding potentially unbeneficial or futile life-sustaining treatments[72].

PROGNOSIS AND OUTCOMES OF SEVERE SEPSIS IN OLDER PATIENTS

There are high mortality rates of around 50%-60% in elderly patients with severe sepsis and septic shock[4,9,73]. The mortality due to severe sepsis in elderly patients is 1.3-1.5 times higher than that in younger cohorts[4,9]. Several studies have found age to be an independent predictor of mortality[4,5,8,9]. Elderly patients with sepsis die earlier during hospitalization and the elderly are more likely to require skilled nursing or rehabilitative care after hospitalization as compared to young adults[4]. Various factors which have been identified as independent predictors of outcome in critically ill patients include[16,73]: (1) Pre-infectious immune or genetic status; (2) Nosocomial events; (3) Co-morbidities; (4) Severity of illness; (5) Age ⩾ 75 years; and (6) Impaired level of consciousness.

The poor prognostic factors in elderly patients with severe sepsis include the presence of shock, elevated serum lactate levels, and presence of organ failure, especially respiratory and cardiac failure[73]. The quality of life after resolution of sepsis is important in formulating health care plans. However, the data regarding subsequent survival and quality of life after an episode of severe

sepsis is limited, especially in the elderly. The elderly are more likely to have poorer functional outcome not only in terms of failure to regain daily living activities, but also in the development of additional functional limitations during the ICU stay[74]. The long-term prognosis of the elderly is chiefly dependent on functional status rather on severity of illness at admission[75]. In a study by Ely *et al*[12], the elderly (≥ 75 years of age) were more likely to be discharged from hospital to a nursing home or alternative health care facility (55%) rather than to home (45%). In another study, age greater than 80 years was found to be an independent predictor of discharge to another healthcare facility rather than to home[76]. Hence, future research in the management of severe sepsis should not only target improved survival, but also good functional outcome in these patients.

HEALTHCARE COSTS AND RATIONING OF RESOURCES

There are huge financial implications in the management of sepsis on limited healthcare resources. Data suggests that the annual cost of sepsis management was $17 billion in the year 2000 alone[5]. Moreover, more than half of this cost was attributable to the care of patients more than 65 years, and around one third to the care of patients more than 75 years of age. The frequency of sepsis is predicted to increase by more than 5% per year along with an increasing elderly population and higher mortality[4]. Hence, management of sepsis in the elderly will have huge financial implications[2,5].

This has led to an intense debate on the rationing of resources, criteria for admission to the ICU and the decision to withdraw or withhold treatment in elderly patients. Denying ICU admission to the elderly has few supporters, however, denying ICU admission and inadequate treatment solely on age is highly controversial[77-82]. There is enough evidence available on the association between increased intensity of treatment and improved survival and good long-term outcome even in the elderly[80,82]. Hence, age only should not be the reason for denying admission or the appropriate management of sepsis in an elderly patient.

AREAS OF FUTURE INVESTIGATIONS

There is a dearth of available data on severe sepsis in the very old, especially regarding factors determining outcome, quality of life and functional outcome after treatment of sepsis. The trials on antisepsis and antimicrobial agents tend to exclude the very elderly, because they are generally believed to be less likely to respond to treatment. However, in order to formulate optimal healthcare policies as the population ages and the number of cases of sepsis increases, future trials should also focus on this age group of patients. Further investigations should also aim to assess the impact of preventive measures and the implementation of bundled strategies in the management of severe sepsis in the elderly.

CONCLUSION

The management of elderly patients in the ICU is always challenging in terms of associated clinical co-morbidities and the greater medical, social and financial resources involved. Severe sepsis and septic shock are not only more common, but are also associated with higher morbidity and mortality in elderly patients. A lower threshold and higher index of suspicion is required to diagnose sepsis in this age group. Timely aggressive and balanced management may improve outcomes in these patients. However, more clinical trials including elderly patients will help to decide appropriate management in the future.

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