Review Article

The hemodynamic management of elderly patients with sepsis

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Abstract Sepsis is among the most common reason for admission to intensive care units (ICU) throughout the world. In the US and most Western nations sepsis is largely a disease of the elderly. Management of elderly patients with severe sepsis is challenging. Early recognition of this syndrome, together with the early administration of appropriate antibiotics and cautious fluid resuscitation is the cornerstone of therapy. Echocardiography together with non-invasive or invasive hemodynamic monitoring is recommended in patients who have responded poorly to fluids or have significant underlying cardiac disease. This paper reviews the hemodynamic changes that characterize sepsis, particularly as they apply to elderly patients and provides recommendations for the management of these patients. (J Geriatr Cardiol 2007;4:120-6.)

Key Words: sepsis; elderly; septic shock; fluids; norepinephrine; activated protein C; corticosteroids; ventricular function; vasopressin; echocardiography; cardiac output

Introduction

Sepsis is among the most common reason for admission to intensive care units (ICU) throughout the world. Over the last two decades the incidence of sepsis in the United States has trebled and is now the tenth leading cause of death. 1, 2 In the United States, approximately 750,000 cases of sepsis occur each year, at least 225,000 of which are fatal. 1, 2 Advances in medical technologies, the increasing use of immunosuppressive agents and the aging of the population have contributed to the exponential increase in the incidence of sepsis. Despite the availability of potent antimicrobial agents and advanced life-support, the case fatality rate for patients with sepsis has remained between 20% and 30% over the last 3 decades. 1, 2

People who are greater than 65 years of age are the fastest growing segment of the US population. 3 By 2030 the population older than 65 years will double to approximately 70 million and the fastest growing segment of the population, those > 84 years will triple. 3, 4 In the US and most Western nations sepsis is largely a disease of the elderly. Martin and colleagues performed an observational study on the effect of age on the development and outcome of adult sepsis. 5 Using national discharge data they reviewed over 10 million adults with sepsis over a 24 year period. Although elderly patients (older than 65 years) accounted for only 12% of the US population they accounted for 64.9% of sepsis cases, yielding a relative risk of 13.1 compared with younger patients. Furthermore while the incidence of sepsis increased linearly with aging the case fatality rate increased exponentially. With the aging of the population and the high incidence of sepsis in this population, the management of sepsis in the elderly has become an important health care issue.

The increased incidence of sepsis in the elderly is likely due to the high prevalence of comorbidities together with changes in the immune system that occur with aging. In the study by Martin, et al, 71% of patients with sepsis had chronic comorbidities, with elderly patients having twice as many co-morbidities as younger patients. It should be noted that pneumonia is the commonest cause of sepsis in elderly patients, most occurring in debilitated patients in chronic health care facilities. 7 Indeed, the incidence of pneumonia increases dramatically with aging, with the risk being almost six times higher in those over the age of 75, compared to those less than 60 years of age. 8- 11 Chronic obstructive pulmonary disease (COPD), heart disease, malignancy, malnutrition, congestive heart failure and diabetes mellitus have been implicated as risk factors leading to pneumonia in the elderly. 11 In addition a diminished cough reflex, dysphagia and poor oral hygiene all increase the risk of elderly patients developing pneumonia. 12 In addition, elderly patients are at an increased risk of developing nosocomial infections. Pneumonia, urinary tract infection, decubitus ulcers and wound infection are the commonest nosocomial infections in these patients. In a study of 3,254 trauma patients, 39% of patients over the age of 65 years developed a nosocomial infection as compared to 17% in the
those less than 65 years of age. In this study, the mortality rate for elderly patients who had nosocomial infection was 28% compared with 5% for younger patients.

A progressive decline in the integrity of the immune system occurs with aging. The age related changes are most evident in the peripheral T cell pool, which show signs of decreased reactivation to challenge with antigens. Several studies have demonstrated that the secretion of interleukin-2 (IL-2) by T cells and the number of IL-2 receptors on T cells are reduced in elderly subjects. The age related changes in the immune system, together with the increased burden of chronic disease may explain the increased incidence of sepsis in the elderly.

**Clinical manifestations of sepsis in the elderly**

Sepsis is a systemic process with a variety of clinical manifestations. The initial symptoms of sepsis are non-specific and include malaise, tachycardia, tachypnea, fever and sometimes hypothermia. Although most patients with sepsis have an elevated white cell count, some patients present with a low white cell count, which in general is a poor prognostic sign. Other clinical manifestations include altered mental status, hypotension, respiratory alkalosis, metabolic acidosis, hypoxemia with acute lung injury, thrombocytopenia, consumptive coagulopathy, proteinuria, acute tubular necrosis, intra-hepatic cholestasis, elevated transaminases, hyperglycemia and hypoglycemia. Patients may present with clinical features of a localized site of infection, such as cough, tachypnea and sputum production due to pneumonia; flank pain and dysuria with urinary tract infection and abdominal pain with intra-abdominal infection. In elderly patients the manifestations of sepsis can be quite subtle, with patients presenting with an altered mental state or an otherwise unexplained respiratory alkalosis. Normothermia or hypothermia is common in elderly patients with sepsis.

**The hemodynamic alteration of sepsis in the elderly**

The effective intravascular volume is reduced in patients with sepsis and is a major factor leading to circulatory instability and collapse. In patients who have been inadequately fluid resuscitated, septic shock may present as a hypodynamic state with a low cardiac output. Multiple factors are responsible for the decreased intravascular volume, including an increase in venous capacitance and venous pooling, a generalized increase in microvascular permeability, increased insensible losses and poor fluid intake. In addition, fluid shifts into the intracellular space due to the increased permeability of the cell membrane to sodium. Systemic arterial vasodilation together with resistance to vasopressor agents is the characteristic hemodynamic finding in patients with sepsis. A number of pathogenetic mechanisms are responsible for “failure of the vascular smooth muscle” including increased production of nitric oxide, activation of K+ channels, decreased synthesis/dys-function of catecholamine receptors and vasopressin deficiency. The systemic vasodilation (decreased afterload) leads to an increase in cardiac output. In more than 90% of patients with septic shock who have been volume loaded to assure the absence of hypovolemia, cardiac output is normal or elevated. Despite the high cardiac output, clinical and experimental studies have demonstrated that sepsis is characterized by biventricular systolic (depressed ejection fraction) and diastolic dysfunction (decreased chamber compliance), with an increase in both end-diastolic and end-systolic volume.

Myocardial depression together with peripheral vasodilation and a reduced systemic vascular resistance are the characteristic hemodynamic features found in patients with sepsis. This characteristic pattern occurs within the first 24 hours of the onset of sepsis. The cardiac output and indices of ventricular function normalize as patients recover from the septic insult, while ventricular function remains depressed (despite inotropic agents) in the non-survivors.

**Age-related changes in the cardiovascular system**

The changes in cardiac function with aging have important implications for the management of elderly patients with sepsis and will be briefly reviewed. Cardiovascular performance impacts on critical illness in the elderly in two ways. First, age is a major risk factor for cardiovascular disease, increasing the likelihood that the elderly patient will have coronary vascular disease and/or cardiac failure. Second, the effect of aging on cardiovascular structure and function has implications for hemodynamic support of the elderly. A substantial lack of cardiac reserve is noted by the age of 70. This lack of reserve may not affect the daily functioning of a “well” older individual, but when this same older person experiences the physiological stress of sepsis the lack of reserve becomes apparent through cardiac dysfunction.

With aging there is a progressive decrease in the number of myocytes and an increase in myocardial collagen content. Autonomic tissue is replaced by connective tissue and fat, while fibrosis causes conduction abnormalities through intranodal tract and the His bundle. These changes result in a decrease in left ventricular ejection fraction and an overall decline in ventricular compliance. Arterial distensibility, the major component of afterload, decreases with aging. Resting cardiac output is maintained despite the increased afterload imposed by the stiffening of the outflow tract. However maximal heart rate, ejection fraction and cardiac output decrease with aging. Ventricular relaxation which is more energy dependent than ventricular contraction, and therefore more oxygen dependent also becomes impaired with aging. Diastolic dysfunction is therefore common in the elderly, particularly in those patients with systemic hypertension.

In younger persons, cardiac output is increased predominantly by increasing heart rate in response to β-adrenergic stimulation. With aging there is a relative “hyposympathetic state” in which the heart becomes less
to improve the outcome of patients with severe sepsis and dose) are immunomodulators which have been demonstrated both activated protein C (APC) and glucocorticoids (moderate inflammatory mediators has uniformly met with failure. However, the reduction in left ventricular compliance results in a reduction of early diastolic ventricular filling and a compensatory increase in flow due to atrial contraction. The contribution of left atrial systole to left ventricular filling increases with age. Atrial fibrillation is therefore poorly handed by elderly patients particularly those with marked diastolic dysfunction.

The cardiac dysfunction with aging is compounded by the high incidence of cardiac disease, especially coronary artery disease, in the elderly. Coronary artery disease may go unrecognized in the elderly, as myocardial ischemia may present with non-specific and atypical symptoms. In the Framingham Heart Study myocardial infarction was unrecognized or silent in greater than 40% of patients over the age of 75 years.

Management strategy

The management of patients with severe sepsis and septic shock is complex requiring multiple concurrent interventions with close monitoring and frequent re-evaluations. The management of elderly patients with septic shock is exceedingly difficult; these patients are best managed in intensive care units by physicians experienced in the management of critically ill septic patients. The reader is referred to the “Surviving Sepsis Campaign guidelines for the management of severe sepsis and septic shock”; these guidelines were developed by a number of international critical care organizations and should serve as the framework for the management of patients with sepsis.

The current strategy for the management of patients with sepsis is largely based on treating or eliminating the source of infection, timely and appropriate usage of antimicrobial agents, hemodynamic optimization, and other physiologic organ supportive measures. Gram negative pathogens and meticillin resistant Staphylococcus aureus (MRSA) are particularly common pathogens in the elderly.

Empiric antimicrobial regimes should take this factor into account. Attempts at down-regulating the pro-inflammatory response with novel agents directed at specific pro-inflammatory mediators has uniformly met with failure. However, both activated protein C (APC) and glucocorticoids (moderate dose) are immunomodulators which have been demonstrated to improve the outcome of patients with severe sepsis and septic shock. Although many practitioners may be reluctant to use APC in elderly patients due to the fear of increased intracranial bleeding, this concern has not been born out clinically. Indeed, data from the PROWESS study indicates that mortality reduction with APC was greater in the elderly with no increased risk of major bleeding.

It has become increasingly apparent that in many patients there is a long delay in both the recognition of sepsis and the initiation of appropriate therapy. This has been demonstrated to translate into an increased incidence of progressive organ failure and a higher mortality. The concept that early aggressive treatment (within the first 6 hours of admission to hospital) of patients with severe sepsis and sepsis shock reduces sequential organ failure and improves survival has been demonstrated in a landmark study by Rivers and colleagues. In this study early aggressive therapy that optimized cardiac preload, afterload, and contractility in patients with severe sepsis and septic shock improved survival.

Hemodynamic management of the elderly septic patient

Intravascular volume expansion

Volume resuscitation is considered the best initial therapy for the cardiovascular instability of sepsis. Hypotension can often be reversed with fluid administration alone. Volume repletion in patients with septic shock produces significant improvement in cardiac function and systemic oxygen delivery, thereby enhancing tissue perfusion. Despite sepsis-induced myocardial depression, cardiac index will improve by 25 to 40% during fluid resuscitation. Fluid administration should be titrated to clinical end points such as the mean arterial pressure, heart rate and urine output. In approximately 50% of septic patients who initially present with hypotension, fluids alone will reverse hypotension and restore hemodynamic stability.

The titration of fluids in the elderly patient is particularly challenging. Elderly patients tolerate volume depletion poorly, yet due to the high incidence of underlying systolic and diastolic heart failure compounded by the changes in ventricular function during sepsis, volume repletion in elderly patients should be cautious. Dobutamine should be considered in patients with depressed left ventricular function (after adequate volume loading).

Although cardiac filling pressures (central venous pressure and pulmonary capillary wedge pressure) as measured using a central venous catheter or pulmonary artery catheter are widely used to predict fluid responsiveness this approach is devoid of supportive data. Indeed, multiple studies have confirmed that both the central venous pressure and pulmonary capillary wedge pressure are unable to predict the hemodynamic response to a fluid challenge.
In mechanically ventilated patients, the magnitude of the respiratory change in left ventricular stroke volume can be used to assess fluid responsiveness. Experimental and clinical studies suggest that large variations (≥~12%) in systolic pressure (SPV) and pulse pressure (PPV) as measured using an arterial catheter, predict an increase in cardiac output with fluid loading. This dynamic test of “recruitable cardiac output” is highly reproducible and simply performed at the bedside.

It needs to be emphasized that the goal of fluid resuscitation is to increase cardiac output and hence tissue oxygen delivery. Fluid administration will only increase cardiac output if the patient is on the steep portion of the Frank-Starling curve. Volume resuscitation, particularly in elderly patients, is therefore a double edged sword as elderly patients tolerate hypovolemia poorly yet excess fluid administration is equally poorly tolerated and likely associated with increased morbidity and mortality. Elderly patients with severe sepsis therefore require very close monitoring of vital signs and indices or organ perfusion. Non-invasive or invasive (pulmonary artery catheterization) hemodynamic monitoring is recommended in those patients who have responded poorly to fluid administration.

**Vasoactive agents**

When an appropriate fluid challenge (2L of crystalloid) has failed to restore adequate blood pressure (MAP > 65 mmHg) and organ perfusion, therapy with vasopressor agents should be started. Vasopressor therapy may also be required to maintain perfusion in the face of life-threatening hypotension, even when a fluid challenge is in progress. Patients with sepsis have a markedly abnormal ventricular response to volume infusion, with a significantly smaller increase in left ventricular stroke work index than controls in response to fluid challenges. Reluctance to optimize hemodynamics with vasopressors may stem from the traditional belief that vasopressors produce adverse vasoconstrictive effects peripherally that outweigh their positive effects on the central circulation. The failure to improve tissue perfusion with vasoactive agents may lead to progressive multi-organ failure and death. However, the true risk-benefit ratio and the optimal choice of inotropic agents in patients with sepsis has yet to be determined in well controlled clinical studies.

Currently norepinephrine remains the first-choice vasopressor agent in patients with septic shock. Although there is no high quality evidence, human and animal studies suggest many advantages of norepinephrine over other vasopressor agents. Norepinephrine has been shown to improve hemodynamic parameters including splanchnic perfusion and tissue oxygen utilization in most patients with sepsis. Despite many practitioners’ concerns, there are no data to indicate that this agent has a deleterious renal effect.

The initiation of low dose vasopressin (0.01-0.04 units/min) should be considered in patients receiving norepinephrine. In septic patients low dose vasopressin markedly increases arterial pressure and enhances the pressor response to catecholamines. Vasopressin acts on V1 receptors on vascular smooth muscle cells causing vasoconstriction. Vasopressin also blocks K_\text{ATP} channels an effect that may restore vascular tone in patients with septic shock. Results from the VASST Study (Vasopressin vs Norepinephrine in Septic Shock Study) suggest a benefit from the early initiation of fixed dose vasopressin (0.03 units/min) in patients receiving norepinephrine (unpublished data).

Dopamine has traditionally been the vasoactive drug of choice in patients with sepsis. However, dopamine may not be the ideal vasopressor for a number of reasons. Tachycardia and tachyarrhythmias are common. Decreased prolactin levels may be particularly important in patients with sepsis, as prolactin is an important immuno-stimulatory hormone. The potential harmful effects of dopamine is supported by the SOAP study which demonstrated an increased risk of death in critically ill patients who received dopamine.

**Conclusion**

Management of elderly patients with severe sepsis is challenging. Early recognition of this syndrome, together with the early administration of appropriate antibiotics and cautious fluid resuscitation is the cornerstone of therapy. Close monitoring is essential. Echocardiography together with non-invasive or invasive hemodynamic monitoring is recommended in patients who have responded poorly to fluids or have significant underlying cardiac disease. Norepinephrine together with low fixed-dose vasopressin is suggested in patients who remain hypotensive despite adequate fluid resuscitation. Dobutamine is recommended in patients with global left ventricular dysfunction.

**References**

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