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Selected Topics: Critical Care Medicine

MANAGEMENT OF SEPSIS DURING THE EARLY "GOLDEN HOURS"

Murugan Raghavan, MD, MRCP (UK),* and Paul E. Marik, MD, FCCP, FCCM†

*Department of Critical Care Medicine, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania and †Division of Pulmonary and Critical Care Medicine, Thomas Jefferson University, Philadelphia, Pennsylvania

Reprint Address: Paul Marik, md, fccp, Chief, Pulmonary and Critical Care Medicine, Thomas Jefferson University, 1015 Chestnut Street, Suite M 100, Philadelphia, PA 19107

□ **Abstract—Severe sepsis and septic shock are common causes of morbidity and mortality. Interventions directed at specific endpoints, when initiated early in the "golden hours" of patient arrival at the hospital, seem to be promising. Early hemodynamic optimization, administration of appropriate antimicrobial therapy, and effective source control of infection are the cornerstones of successful management. In patients with vasopressor-dependent septic shock, provision of physiologic doses of replacement steroids may result in improved survival. Administration of drotrecogin alfa (activated), (activated protein C) has been shown to improve survival in patients with severe sepsis and septic shock who have a high risk of mortality. In this article we review the multi-modality approach to early diagnosis and intervention in the therapy of patients with severe sepsis and septic shock. © 2006 Elsevier Inc.**

□ **Keywords—severe sepsis; septic shock; sepsis syndrome; critical illness; early resuscitation; golden hour**

INTRODUCTION

In recent decades the reported incidence of sepsis has increased dramatically, largely due to the advancing age of the population, an increased number of invasive procedures performed, and immunosuppressive therapy (1–3). Sepsis is among the most common reasons for admission to intensive care units throughout the world (4). In the United States alone, approximately 750,000 cases of sepsis occur each year, at least 225,000 of which are fatal (2). Sepsis is now the 10th leading cause of death in the United States (2,5). Despite the use of antimicrobial agents and advanced life-support care, the case fatality rate for patients with sepsis has remained between 30% and 50% over the past three decades (3,6). Survivors of sepsis and septic shock are observed to have a higher 6- and 12-month mortality rate and a significantly lower health-related quality of life (7,8). Recent advances in understanding the pathophysiology of sepsis have led to the evolution of newer therapies that have demonstrated surprising efficacy (9–15). The current systematic review closely focuses on evidence-based recommendations, made by the Society of Critical Care Medicine's Surviving Sepsis Campaign 2004 guidelines (16). In addition, we also performed literature search using terms such as "severe sepsis, septic shock, sepsis syndrome, critical illness," and "early resuscitation" using the Medline database from 1960 to the present, and have attempted to include major clinical trials and other systematic reviews published in this field.

SEPSIS PATHOPHYSIOLOGY

When the body is challenged by foreign microbial agents, homeostatic mechanisms come into play that attempt to rid the body of the foreign agent without

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damaging the host. This involves the activation of pro- and anti-inflammatory pathways, which are tightly controlled and regulated (17). In most individuals, the body is able to achieve a balance between pro-inflammatory and anti-inflammatory mediators and homeostasis is restored. In some patients, however, this balance is upset with an excessive pro-inflammatory response resulting in systemic inflammatory response syndrome (SIRS), multi-system organ dysfunction, septic shock and, ultimately, death (17–20).

The constellation of abnormalities that characterize severe sepsis and septic shock includes circulatory dysfunction with intravascular volume depletion, peripheral vasodilatation, myocardial depression, and a diffuse microcapillary injury leading to hypoperfusion of vital organ vascular beds (21–24). This occurs in the setting of a hypermetabolic state resulting in an imbalance between oxygen delivery and demand leading to tissue hypoxia. This may be further complicated by cytopathic hypoxia due to sepsis-induced mitochondrial dysfunction (25,26). Tissue hypoxia is assumed to be the key factor leading to multi-organ failure and death (17,27). Thus, early aggressive resuscitation of the septic patient may limit or reverse tissue hypoxia and the progression to organ failure. This transition to organ failure occurs during the critical "golden hours," when time is survival, and the definitive recognition and treatment of sepsis provides maximal benefit in terms of outcome (9). These golden hours may elapse in the Emergency Department (ED), hospital ward, or the intensive care unit (ICU) (28–30). Lundberg and coworkers demonstrated that for patients with septic shock on the hospital wards, there were clinically important delays in the transfer of patients to the ICU, reception of intravenous fluid boluses, and reception of inotropic agents, which had implications for increased mortality (29).

Current management of sepsis includes early hemodynamic optimization with other physiologic organ supportive measures, timely and appropriate usage of antimicrobial agents, and treating or eliminating the source of infection. Attempts at down-regulating the pro-inflammatory response with novel agents directed at specific pro-inflammatory mediators has uniformly met with failure (17,31–34). Recently several modalities including activated protein C and stress doses of glucocorticoids have been demonstrated to decrease mortality in critically ill septic patients (9–11,20,35–37).

DIAGNOSIS OF SEVERE SEPSIS AND SEPTIC SHOCK

Sepsis is a systemic process with a myriad of clinical manifestations. The initial symptoms of sepsis are nonspecific 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, intrahepatic cholestasis, elevated transaminases, hyperglycemia, and hypoglycemia (see Table 1).

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 complicated urinary tract infection; and abdominal pain with intra-abdominal infection. The manifestations of sepsis sometimes can be quite subtle, particularly in the very young, the elderly, and those with chronic debilitating or immunosuppressing conditions. These patients may present with normothermia or hypothermia. The failure to generate a temperature greater than 37.5°C (99.6°F) in the first 24 h of clinical illness has been associated with an increased mortality rate (38,39). An altered mental state or an otherwise unexplained respiratory alkalosis may be the presenting feature of sepsis.

The signs and symptoms of systemic inflammation are not useful in distinguishing infectious from noninfectious causes of SIRS. Furthermore, a bacterial pathogen is not isolated in all patients with sepsis. Consequently, a number of markers have been evaluated as more specific indicators of infection (40,41). Tools such as procalcitonin (PCT) may be useful and have been shown to be superior to other inflammatory markers such as TNF-α, IL-6, IL-1, and C-reactive protein (CRP) in outcome

Table 1. Criteria for Organ Systems Dysfunction during Severe Sepsis and Septic Shock

Cardiovascular
SBP $\leq$ 90 mm Hg or MAP $\leq$ 70 mm Hg for at least 1 h despite adequate fluid resuscitation
Vasopressor use
Renal
Urine output $<$ 0.5 ml/kg /h for 1 h, despite adequate fluid resuscitation
Respiratory O_2
$PaO_2/FiO^2 < 250$ in the presence of other organs or systems failure or
$<$200 if the lung is the only dysfunctional organ
Hematologic
Platelet count $<$ 80,000/mm^3 or $\downarrow$ by 50% in the preceding 3 days
Unexplained metabolic acidosis
pH $<$ 7.30 or base deficit $>$ 5.0 mmol/L
Lactate level $>$1.5 times normal

SBP = systolic blood pressure; MAP = mean arterial pressure.