

# HOSPITAL PHYSICIAN®

## CRITICAL CARE MEDICINE BOARD REVIEW MANUAL

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The *Hospital Physician Critical Care Medicine Board Review Manual* is a study guide for fellows and practicing physicians preparing for board examinations in critical care medicine. Each manual reviews a topic essential to the current practice of critical care medicine.

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# Septic Shock

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## INTRODUCTION AND DEFINITIONS

Severe sepsis and septic shock affect over 750,000 people in the United States each year, resulting in over 200,000 deaths.<sup>1</sup> Recent work by Martin and colleagues<sup>2</sup> indicates that the incidence of sepsis is increasing; however, the overall case fatality rate may be decreasing. With the ageing population in the United States, the incidence of sepsis is expected to continue to rise. This monograph discusses current definitions of sepsis, reviews key components of the pathophysiology of sepsis, and presents an organized approach to management of severe sepsis and septic shock.

Sepsis begins with an insult that sets off an inflammatory response. This response may progress through a continuum which, at worst, may culminate in multisystem organ dysfunction and death. Definitions of conditions comprising the sepsis continuum were proposed by Bone and colleagues<sup>3</sup> in 1992 (Table 1). While the definitions help provide an organized understanding of the continuum of sepsis, certain limitations do exist. In general, the definitions may be overly sensitive and non-specific. In addition, several of the defined states may be subject to interpretative variability, such as the concept of septic shock being defined as “hypotension despite adequate fluid resuscitation.” Physicians may differ considerably on how they define “adequate fluid resuscitation.” Thus, a patient may be placed on vasopressors after 1 to 2 L of fluid (ie, septic shock) under the care of one physician, whereas a second physician may choose to administer 5 to 6 L of fluid to the same patient and never initiate vasopressor support (ie, severe sepsis). Therefore, the definition of septic shock may reflect the treatment pathway taken by a physician rather than the physiology of a patient. Additionally, a strict definition of shock based on blood pressure fails to acknowledge that severe tissue hypoperfusion may exist in the presence of adequate pressure. Despite these limitations, the definitions are widely utilized in the clinical arena and particularly in research. While change may occur in the future, Rangel-Frausto and colleagues,<sup>4</sup> in part, validated the continuum of the definitions by showing a general incremental increase in mortality with progressive disease (Figure).

## PATHOPHYSIOLOGY

Sepsis encompasses a complex inflammatory reaction to infection that includes derangements in coagulation, immune function, endothelial function, and tissue oxygenation. Sepsis begins with a source of infection that leads to a generalized and oftentimes exaggerated inflammatory response. In approximately 25% of cases, cultures may be negative and a source of infection is not readily identifiable.<sup>4</sup> Nevertheless, cellular components of whatever pathogens are present cause monocytes, neutrophils, and macrophages to generate cytokines and other immune mediators that activate the complement system and promote neutrophil activity against the pathogen. Foremost of the cytokines are the interleukins, particularly the interleukin (IL)-1 family and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ). Other mediators include arachidonic acid metabolites, HMGB-1, and platelet-activating factor.

In certain instances, activation of inflammatory mediators can be profound and may correlate directly with mortality. Elevated TNF- $\alpha$  in sepsis caused by *Neisseria meningitidis* infection is an example of a cytokine-disease interaction that significantly correlates with mortality.<sup>5</sup> However, pinpointing specific cytokine elevations as being causative of end-organ damage is typically not possible, and markedly elevated measurable levels of specific cytokines are the exception rather than the norm. Several studies have noted that only 10% to 20% of patients have detectable elevated levels of TNF- $\alpha$  or IL-1.<sup>6,7</sup> To that end, efforts to pharmacologically block TNF- $\alpha$  have generally failed to improve mortality in the majority of patients with severe sepsis.

The cardiovascular and endothelial effects of immune mediators may become detrimental to tissue oxygen delivery in severe sepsis. TNF- $\alpha$  and IL-1 are associated with increased nitric oxide levels that cause vasodilation and myocardial suppression. Mediators such as complement and bradykinin cause systemic vasodilation, hyperemia, and increased endothelial permeability. Polymorphonuclear leukocytes directly contribute by releasing reactive oxygen species, other vasodilatory agents, and proteolytic enzymes in the