The definition of septic shock: implications for treatment

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ABSTRACT

Sepsis is among the most common reasons for admission to intensive care units throughout the world. In 1991, a new set of terms and definitions was developed to define sepsis more precisely. The concept of the "systemic inflammatory response syndrome" (SIRS) was developed, and its diagnostic criteria were defined. Sepsis was defined as suspected or microbiologically proven infection together with SIRS, while severe sepsis was defined as sepsis together with sepsis-induced organ dysfunction. Septic shock was defined as sepsis-induced *hypotension* persisting despite *adequate fluid resuscitation*. Data from recently published trials support this hierarchical stratification, with the mortality from sepsis ranging from 10% to 15%, severe sepsis from 17% to 20%, and septic shock from 43% to 54%. The distinction between severe sepsis and septic shock is critically important as it stratifies patients into groups with a low and a high risk of dying, respectively. However, currently the diagnostic criteria of septic shock remain vague.

We suggest that septic shock is best defined by a systolic blood pressure less than 90 mmHg (or a fall in systolic blood pressure of > 40 mmHg), or a mean arterial pressure less than 65 mmHg after a crystalloid fluid challenge of 30 mL per kg body weight in a patient with severe sepsis. We believe that a vasopressor should be initiated in patients who remain hypotensive after this fluid challenge. The above operational definition of septic shock is important, as it clearly and unambiguously defines in which patients, and when, treatment with a vasopressor should be initiated, and in which patients adjunctive therapy with hydrocortisone and drotrecogin alfa (activated) should be considered.

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Sepsis is among the most common reasons for admission to intensive care units throughout the world.[1-5] Advances in medical technology, the increasing use of immunosuppressive agents, and the ageing of the population have contributed to the dramatic increase in the incidence of sepsis. Over the past two decades, the incidence of sepsis in the United States has trebled, and it is now the 10th leading cause of death.[2,3] In the US, the incidence of severe sepsis has been estimated at 3.0 cases per 1000 population per year, or about 750 000 cases with over 225 000 deaths annually.[2] The incidence of severe sepsis appears to be lower in Europe and in New Zealand and Australia, with an incidence of between 0.51 and 0.77 cases per 1000 population.[4,5]

Definitions

Sepsis originally meant "putrefaction", a decomposition of organic matter by bacteria and fungi. A wide variety of definitions have since been applied to sepsis, including sepsis syndrome, severe sepsis, bacteraemia, septicaemia and septic shock.[6,7] In 1991, the American College of Chest Physicians and the Society of Critical Care Medicine developed a new set of terms and definitions to define sepsis in a more precise manner.[8] The definitions take into account the findings that sepsis may result from a multitude of infectious agents and microbial mediators, and that it may not be associated with detectable bloodstream infection. The term "systemic inflammatory response syndrome" (SIRS) was coined to describe the common systemic response to a wide variety of insults. When SIRS was the result of a suspected or confirmed infectious process, it was termed sepsis. Severe sepsis was defined as sepsis plus organ dysfunction. Septic shock is a subset of severe sepsis and was defined as sepsis-induced *hypotension* persisting despite *adequate fluid resuscitation*.

Hierarchical host response

Three stages in the hierarchy of the host response to infection were therefore recognised: sepsis, severe sepsis and septic shock, with sepsis having the best prognosis, and septic shock the worst. Data from recently published trials support this postulate, with the mortality from sepsis ranging from 10% to 15%, severe sepsis from 17% to 20%, and septic shock from 43% to 54%.[1,9-13] The distinction between severe sepsis and septic shock is critically important, as it stratifies patients into groups with a low and a high risk of dying, respectively. It also suggests that a more aggressive treatment strategy may be indicated in patients with septic shock. It is therefore surprising that a standardised operational definition of septic shock does not exist. Notably, the *Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock* neither define septic shock nor stratify treatment based on this diagnosis, possibly because of the current lack of a universally acceptable definition for this entity.[14]

Septic shock and fluid boluses

Septic shock has been variably defined as refractory shock, or hypotension refractory to volume replacement.[6,15-19] However, neither the blood pressure level that defines hypotension, nor the volume and type of replacement fluid required before the diagnosis can be made have been standardised. Based on recent publications, we suggest that septic shock is best defined by a systolic blood pressure less than 90 mmHg (or a fall in systolic blood pressure of > 40 mmHg), or a mean arterial pressure less than 65 mmHg after a crystalloid fluid challenge of 30 mL per kg body weight over 30 minutes in patients with sepsis and in the absence of other causes for hypotension.[20,21] While an initial fluid bolus ranging from 250 to 1000 mL has been suggested, we believe, based on the estimated fluid deficit in patients with sepsis, that this is inadequate volume resuscitation.[19-24] In a patient previously known to have low baseline blood pressure, septic shock is best defined as a 30% or greater drop in the mean arterial pressure. These criteria are unambiguous and should therefore allow intensified early goal-directed therapy in the group of patients who are at the highest risk of dying from sepsis.[14,20]

Septic shock and vasopressors

While volume replacement is the cornerstone of resuscitation in patients with sepsis, volume replacement alone may not always achieve an adequate perfusion pressure (mean arterial pressure > 65 mmHg) in patients with septic shock.[21,25] Reluctance to optimise haemodynamics with vasopressors may stem from the mistaken belief that vasopressors produce adverse vasoconstrictive effects on the renal and splanchnic beds.[26,27] The failure to improve tissue perfusion with vasoactive agents may lead to progressive multiorgan failure and death.[28,29] The time to begin a vasopressor agent has not been clearly defined. We believe that a vasopressor should be initiated in patients who remain hypotensive after the 30 mL per kg fluid challenge (ie, patients who meet the criteria for septic shock).[21,25] Volume resuscitation (with crystalloid or colloid) should continue while the dose of vasopressor is being titrated, until an adequate perfusion pressure is achieved, and tissue perfusion is optimised.[14,21] However, the true risk–benefit ratio and the optimal choice of vasopressor agent(s) in patients with sepsis have yet to be determined in well controlled clinical studies.

Corticosteroids, activated protein C and septic shock

"Moderate-dose" (200–300 mg/day) hydrocortisone has been shown to result in more rapid reversal of shock (vasopressor dependency) in patients with septic shock.[30] The benefit of hydrocortisone in terms of survival is less clear[31] (unpublished data from the CORTICUS [Corticosteroid Therapy of Septic Shock] study, presented at the 19th Annual Congress of the European Society of Intensive Care Medicine, Barcelona, 2006). Moderate-dose hydrocortisone should therefore be considered in the treatment strategy for patients with septic shock. The role of corticosteroids in patients with severe sepsis remains to be determined.[30] Patients with septic shock may also be candidates for treatment with drotrecogin alfa (recombinant activated protein C). Drotrecogin alfa (activated) has been demonstrated to reduce mortality, largely in patients with septic shock rather than in those with sepsis or severe sepsis (ADDRESS [Administration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis] study).[32] We believe that, in patients with sepsis, therapeutic decisions should not be based on the APACHE II score or similar severity of illness scoring systems.[33,34] These scoring systems were designed to compare the severity of illness of groups of ICU patients and not individual patients. Furthermore, these scores are based on the most deranged physiological variable in the 24-hour period after ICU admission and therefore cannot be computed early in the patient's hospital course. The lack of reliability of these scores is compounded by the inter- and intra-observer variability in their computation.[34]

Conclusions

In summary, we define septic shock as a systolic blood pressure less than 90 mmHg (or a fall in systolic blood pressure of > 40 mmHg) or a mean arterial pressure less than 65 mmHg after a crystalloid fluid challenge of 30 mL per kg body weight in patients with sepsis, and in the absence of other causes for hypotension.[20,21] In a patient previously known to have a low baseline blood pressure, septic shock is best defined as a 30% or greater drop in the mean arterial pressure. We believe that this operational definition of septic shock is important, as it clearly and unambiguously defines in which patients, and when, treatment with a vasopressor should be initiated, and when adjunctive treatment with hydrocortisone and drotrecogin alfa (activated) should be considered. Furthermore, this definition allows risk stratification of patients with sepsis within the first hour after arrival in the emergency department and therefore facilitates early goal-directed therapy.[20]

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