Management of severe sepsis

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Abstract

Severe sepsis is a heterogenous condition affecting multiple organ systems, and is commonly encountered in the hospital setting due to both community and nosocomial infections. Although the incidence of severe sepsis has increased over the past decades, there is evidence that mortality in developed world settings has improved. Management of the septic patient involves rapid evaluation and prompt initiation of both supportive and specific therapies. Such patients commonly require admission to the intensive care unit (ICU) for invasive monitoring and haemodynamic support. Resuscitation, early initiation of broad-spectrum antimicrobial therapy and source control remain the cornerstones of therapy. Recent studies have shown no benefit to early goal-directed therapy or albumin as a resuscitation fluid, while hydroxyethyl starches have been shown to be harmful. Corticosteroids remain a controversial therapy. This review summarizes the contemporary evidence regarding diagnostic and treatment strategies of severe sepsis, with emphasis on patients in critical care settings.

Keywords Complications; infection; intensive care; outcomes; septic shock; severe sepsis; treatment

Royal College of Anaesthetists CPD Matrix: 2C03

Learning objectives

After reading this article, you should be able to:

- define and differentiate sepsis according to degrees of severity, and assign management strategies accordingly
- outline an approach for assessment and initiation of therapy in patients with suspected severe sepsis
- understand the treatment options for severe sepsis, including the evidence for and against ancillary therapies such as corticosteroids
- acknowledge the diagnostic challenges of the intensive care patient, and develop a strategy for the empirical management of occult infection

Definitions

The term sepsis signifies infection giving rise to a systemic inflammatory response in the host. The varying degrees of sepsis are defined by the host response to infection, ranging from uncomplicated fever and leukocytosis to refractory hypotension and multi-organ failure (Table 1).

Epidemiology

Severe sepsis accounts for 3% of hospital presentations and 11–14% of intensive care unit (ICU) admissions. Furthermore the overall incidence has increased in the last 30 years. Of hospitalized patients with severe sepsis, around half are admitted to ICU during their admission. Severe sepsis is associated with increased ICU and hospital length-of-stay. In-hospital mortality remains substantial but has declined over the past decades, from between 35–47% and 18–30%.[1] Causes for the reduction in mortality are unclear but are likely multi-factorial with overall improvements in intensive care, and attention to early identification and management of sepsis.

Pathophysiology of severe sepsis

A prototypic physiological response to infection involves an inflammatory response, which over time evolves into an anti-inflammatory state. The systemic inflammation and organ dysfunction of severe sepsis arise from interactions between microbe, innate and adaptive immune cells. Details of the cellular mechanisms are beyond the scope of this article but the interested reader should read the review by Angus and van der Poll.[2]

Risk factors for healthcare-associated sepsis

Patients in hospital are at risk of nosocomial infections that result in prolonged admissions, higher mortality, and constitute a considerable cost burden. Management of hospital-acquired infections requires attention to specific risk factors:

1. Patient factors, e.g. immunosuppression-associated comorbidity or therapy
2. Microbe factors, i.e. presence of multi-resistant or virulent bacteria in hospital
3. Procedural risks, i.e. surgery, indwelling catheters or implantable devices

Management

Early, aggressive management of the patient with severe sepsis reduces mortality and organ dysfunction. Rapid identification of the infective foci as well as obtaining microbiological specimens should occur concurrently with the initiation of supportive therapy. Observational studies suggest significant reductions in mortality with earlier introduction of antibiotics; therefore empirical antimicrobials should not be withheld while awaiting identification of a pathogen.

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Definitions of different degrees of severity of sepsis

Condition	Description
SIRS	At least two of the following conditions: • temperature >38.5 °C or <35.0 °C; • heart rate of >90 beats/min; • respiratory rate of >20 breaths/min or $PaCO_2$ of <32 mmHg; • WBC count of >12,000 cells/ml, <4000 cells/ml, or >10% immature (band) forms
Sepsis	SIRS in response to confirmed or presumed infection
Severe sepsis	Sepsis and at least one of the following signs of organ hypoperfusion or dysfunction: • areas of mottled skin, capillary refilling of >3 seconds; • urinary output of <0.5 ml/kg/hr or renal replacement therapy; • lactate >2 mmol/L; • change in neurological status; • platelet count of <100,000 cells/ml or DIC; • acute lung injury/ARDS; • cardiac dysfunction
Septic shock	Severe sepsis and at least one of the following conditions: • MAP of <60 mmHg after intravenous fluid (20–40 ml/kg) or PCWP between 12 and 20 mmHg; • need for dopamine >5 mcg/kg/min, or noradrenaline or adrenaline <0.25 mcg/kg/min to maintain MAP >60 mmHg
Refractory septic shock	Need for dopamine >15 mcg/kg/min, or noradrenaline or adrenaline >0.25 mcg/kg/min to maintain MAP >60 mmHg

Abbreviations: SIRS, systemic inflammatory response syndrome; WBC, white blood cell; DIC, disseminated intravascular coagulation; ARDS, acute respiratory distress syndrome; MAP, mean arterial pressure.

Table 1

The Surviving Sepsis Campaign comprehensively reviews the sepsis-related literature and provides recommendations according to level of evidence.[3]

Initial assessment and resuscitation

Severe sepsis can present with multi-organ failure and respiratory collapse. The first priority in any patient with suspected severe sepsis is assessment of their airway and adequacy of breathing, followed by evaluation of end-organ perfusion.

Fluid resuscitation

Intravenous fluid resuscitation (20–40 ml/kg) is commonly recommended in any patient with suspected sepsis causing hypotension or an elevated serum lactate. The choice of crystalloid or colloid composition has been controversial. While a subgroup analysis of the Saline versus Albumin Fluid Evaluation (SAFE) study suggested that resuscitation with 4% albumin (a colloid) may reduce mortality in patients with severe sepsis, further studies including a recent meta-analysis have not supported this finding.[4] Hydroxyethyl starch (HES) colloids increase rates of acute kidney injury when compared to normal saline[5] and increase mortality when compared to balanced crystalloids,[6] and the US Food and Drug Administration advises that HES solutions should not be used in critically ill patients. Gelatin-based colloids have not been rigorously evaluated in multi-centre randomized controlled trials.

Early goal-directed therapy

A single-centre, unblinded trial by Rivers et al. demonstrated a reduction in mortality associated with a strategy thereafter known as early goal-directed therapy (EGDT). In the 6 hours following presentation the EGDT targets were central venous pressure (CVP) of 8–12 mmHg, mean arterial pressure (MAP) ≥65 mmHg, central venous oxygen saturations ≥70% and haematocrit ≥30%.[7] On the basis of this study, these targets with the addition of urine output ≥0.5 ml/kg/hr were promoted by the Surviving Sepsis Campaign. However, two multicentre, randomized controlled trials have since failed to replicate the mortality benefit with EGDT. The Protocolized Care for Septic Shock (ProCESS) trial enrolled 1341 patients in the United States and compared the EGDT protocol to a protocol that did not mandate invasive monitoring and to non-protocolized care. No differences in mortality, organ dysfunctions, duration of organ support or incidence of adverse events were seen between the groups.[8] The Australasian Resuscitation in Sepsis Evaluation (ARISE) trial enrolled 1600 patients and compared the EGDT protocol to standard care in 51 centres, mostly in Australia and New Zealand. The EGDT group had significantly higher rates of vasopressor use but there were no differences in mortality or in the use or duration of other organ supports.[9] In response to these trials, the Surviving Sepsis Campaign no longer requires the measurement of CVP or central venous saturation as part of its treatment bundles but noted EGDT does not appear to be harmful. These changes are anticipated to be included in the next published guidelines.

Vasoactive agents

Vasopressors are frequently used to maintain a mean arterial pressure (MAP) of at least 65 mmHg in persistently hypotensive patients following intravenous resuscitation. Although different agents have theoretical advantages, there is no evidence that any one vasoactive agent confers a survival benefit over another.