Chapter 16
Severe Sepsis

Suhel Al-Soufi and Vineet Nayyar

Key Points
- The cornerstones of sepsis management are recognition, haemodynamic optimisation, early and appropriate antibiotic therapy, organ-specific support and adjuvant therapy.
- Fluid management of septic patients is time sensitive.
- Mean arterial pressure (MAP) of at least 65 mmHg should be targeted in patients with septic shock.
- Timely administration of antibiotic therapy, (preferably within 1 h of recognition of severe sepsis) is associated with improved outcome in life-threatening infections.

Introduction

Sepsis is a clinical syndrome resulting from the host response to microbial invasion that is still incompletely understood. Sepsis, severe sepsis, and septic shock are commonly considered as a continuum of body's response to the presence of an infection (Table 16.1); however, severe sepsis or septic shock can be diagnosed

S. Al-Soufi, MD, DEAA, EDIC, FCICM
Intensive Care Unit, St Vincent's Hospital, Darlinghurst, NSW 2010, Australia
e-mail: Suhelsoufi@gmx.de

V. Nayyar, MBBS, MD, DNB, MPH, FRACP, FCICM (✉)
Intensive Care Unit, Westmead Hospital, Westmead, NSW 2145, Australia
e-mail: Vineet.Nayyar@health.nsw.gov.au

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Table 16.1 Definitions of sepsis, severe sepsis and septic shock

Infection
The presence of pathogenic or potentially pathogenic microorganisms at a site normally considered sterile
Bacteraemia
The presence of viable bacteria in the blood
Sepsis
Host response as the result of proven or suspected infection
Host response manifested by 2 or more of the following:
Temperature >38.3 or <36 °C
Heart rate >90 per min
Respiratory rate >20 per min or pCO_2 <32 mmHg
White cell count >12,000 or <4,000 or >10 % band forms
Severe sepsis
Sepsis associated with organ dysfunction, manifested as:
Hypotension (systolic BP <90 mmHg or mean arterial pressure <70 mmHg)
Oliguria (<0.5 ml/kg per h urine output)
Hypoxaemia (PaO_2/FiO_2 ratio <250)
Lactate above upper limit of laboratory normal
Altered mental state
Septic shock
Sepsis associated with hypotension (mean arterial pressure <70 mmHg) despite adequate fluid resuscitation
Multi-organ dysfunction syndrome (**MODS**)
Presence of altered organ function in an acutely ill (often septic) patient; such homeostasis cannot be maintained without intervention

without accompanying evidence of infection. Sepsis is the most common cause of death in intensive care (ICU) patients all over the world with mortality rates of 35 % or higher amongst the worst affected cases.

Aetiology

Bacteria are the most common causative agents of septic shock, with roughly even numbers of infections due to Gram-positive and Gram-negative organisms. Sometimes, nonbacterial organisms like fungi, viruses or parasites are the cause of severe sepsis and multi-organ dysfunction. In approximately one-third of patients, causative organisms are never isolated possibly because of prior exposure to antibiotics.

Pathogenesis and Physiological Disturbances

- The hallmark of sepsis is a decrease in systemic vascular resistance that occurs despite increased levels of endogenous catecholamines. Decrease in vascular tone affects both the arterial and the venous side of circulation.
- Additionally, diffuse endothelial injury results in a vascular leak with oedema formation and intravascular fluid depletion.
- Myocardial dysfunction also occurs in patients with septic shock and takes the form of decreased myocardial compliance and stroke volume. Compensation by way of increased heart rate is sustained only in those with no pre-existing cardiac disease.
- Even before the onset of haemodynamic instability, patients manifest features of poor tissue perfusion due to maldistribution of blood and microvascular obstruction.

Clinical Features

Sepsis produces at least three categories of clinical manifestations (Table 16.2). These are sometimes superimposed on signs and symptoms of pre-existing disease or therapy-related effects.

- First, patients usually manifest signs and symptoms related to the primary focus of infection. A careful history and physical examination often leads to the probable site of infection. It is important to examine the skin, wounds, throat, nose, sinuses and optic fundi as these may hold valuable clues to the diagnosis.
- Second, patients manifest one or more non-specific signs of sepsis such as fever, tachypnoea or tachycardia. A small percentage of septic patients, particularly the elderly, present with hypothermia. Certain laboratory abnormalities are incorporated in the diagnostic criteria for sepsis (Table 16.1), but these have a poor sensitivity and specificity.
- Lastly, septic patients present with evidence of organ dysfunction or complications. Sepsis-induced hypotension is common and is associated with oliguria, metabolic acidosis, hyperlactataemia and acute kidney injury (AKI). Altered mental state can be a presenting feature in the elderly. Isolated thrombocytopaenia without overt laboratory evidence of disseminated intravascular coagulopathy (DIC) is seen in up to half of the patients. Acute respiratory distress syndrome (ARDS) develops in 30 % of patients.

Table 16.2 Clinical features of sepsis

General signs and symptoms
Fever/hypothermia
Tachypnoea
Tachycardia
Significant oedema
Hyperglycaemia
Inflammatory reaction
Altered white cell count
Increased C-reactive protein
Raised levels of biomarkers
Haemodynamic alterations
Arterial hypotension
Tachycardia
Increased cardiac output
Altered skin perfusion
Low systemic vascular resistance
Signs of organ dysfunction
Hypoxaemia
Oliguria or rise in creatinine
Coagulation abnormalities
Altered mental state
Thrombocytopaenia
Altered liver function
Intolerance to feeding
Tissue perfusion abnormalities
Hyperlactataemia (>2 mmol/L)
Decreased capillary refill or mottling

Management

Haemodynamic Management

Early Goal-Directed Therapy

Early goal-directed therapy (EGDT) targets predefined physiological goals of central venous pressure, mean arterial pressure, urine output and central venous or mixed venous oxygen saturation with protocol-driven fluid resuscitation, use of vasopressors and dobutamine and red cell transfusion [1]. International guidelines such as the Surviving Sepsis Campaign have advocated EGDT as a standard of care [2]. Two recent large, multicentre studies have led to a reappraisal of these recommendations. In the Australasian Resuscitation in Sepsis Evaluation (ARISE) study, EGDT compared with usual care, did not reduce 90-day all-cause mortality amongst patients presenting with early septic shock [3]. Similarly, in the randomised multicentre Protocolized Care for Early Septic Shock (ProCESS) trial, a

combination of EGDT and protocol-based therapy for patients in whom septic shock was diagnosed in the emergency department was not associated with a survival benefit, as compared with usual care [4]. Taken together, it appears that protocol-based resuscitation does improve outcomes of patients who were identified as having septic shock in the emergency department, but similar outcomes were also obtained by clinicians acting promptly and directing elements of patient care using their own clinical judgment.

Colloids or Crystalloids

Aggressive fluid resuscitation is the mainstay of initial haemodynamic management of severe sepsis. As the physiological volume of distribution is much larger for crystalloids compared to colloids, resuscitation with colloids requires less volume to achieve the same end points. This notwithstanding, mortality is not significantly different when unselected colloids are compared with crystalloids [5]. More than a decade ago, the Saline versus Albumin Fluid Evaluation (SAFE) study [6] compared albumin and saline in ICU patients and showed no difference in mortality. However, a subgroup analysis showed a trend towards improved survival amongst septic patients resuscitated with albumin. The Albumin Italian Outcome Sepsis (ALBIOS) study [7] demonstrated that in patients with severe sepsis, albumin replacement in addition to crystalloids did not increase survival despite improvements in haemodynamic variables. Interestingly, a post hoc subgroup analysis of patients with septic shock at the time of enrolment showed significantly lower mortality at 90 days in the albumin group compared to the crystalloid group. Therefore, albumin could be considered for patients with septic shock in whom its use might improve short-term haemodynamic indices. On the other hand, there is compelling evidence that resuscitation with hydroxyethyl starch (HES) solutions is associated with an increased use of renal replacement therapy without demonstrable benefit when compared with saline [8].

Thus, the use of crystalloids has found a revival. Balanced fluids like lactated Ringer's or Plasma-Lyte have an electrolyte composition close to plasma and do not contribute as much to the generation of metabolic acidosis as 0.9 % saline, which has in fact, a non-physiological sodium and chloride content. The optimal volume of resuscitation fluid is unknown, but approximately 30 mL/kg administered rapidly in well-defined aliquots has been recommended. Multiple studies have demonstrated potential harm with liberal fluid resuscitation, notably when given beyond the initial hours of resuscitation. Venous pooling and hypo-proteinaemia during a septic episode contribute to the formation of tissue oedema, particularly in the lungs, the myocardium and the abdominal compartment, and are considered detrimental. Unfortunately, almost all of the data on fluid accumulation in critically ill patients is retrospective in nature and points only to associative rather than causal relationships [9]. One notable exception is the Fluid and Catheter Therapy Trial (FACTT), a multicentre, randomised clinical comparison of two fluid management strategies, which showed that in the setting of acute lung injury, a more conservative

strategy reduced the duration of ventilation and length of stay in ICU, albeit without demonstration of a mortality difference [10].

Overall, it appears that early aggressive fluid resuscitation should be followed by a more restrictive fluid management to prevent excessive fluid accumulation.

Vasoactive Agents

When the mean arterial pressure (MAP) falls below the autoregulatory threshold of the heart, brain and kidneys, blood flow to organs decreases in an almost linear fashion. Observational studies have demonstrated that a MAP of less than 60–65 mmHg is associated with an increased risk of kidney injury and death. As a result of a shift in the autoregulatory range in patients with chronic hypertension, a higher MAP may be required in these patients. The recent SEPSISPAM trial targeting a MAP of 80–85 mmHg, as compared with 65–70 mmHg, did not result in significant differences in mortality at either 28 or 90 days. However, in the a priori planned subgroup analysis of patients with or without hypertension, the incidence of renal dysfunction was greater with lower MAP target amongst patients with hypertension [11].

Noradrenaline is the predominant endogenous sympathetic amine, which increases MAP by arterial vasoconstriction, augmented myocardial contractility and venoconstriction. There is no compelling evidence to substitute or even supplement the administration of noradrenaline with another vasoactive substance for the majority of patients with septic shock. Adrenaline remains popular in income-poor countries where it is widely available at a fraction of the cost of noradrenaline. Multicentre randomised controlled trials of adrenaline versus noradrenaline in septic shock have not reported a difference in primary or secondary outcomes, only a significant difference in the incidence of tachycardia, lactic acidosis and insulin requirements [12]. The Surviving Sepsis Campaign guidelines suggest that vasopressin 0.03 units/min can be added to noradrenaline with the intent of either raising MAP or decreasing noradrenaline dosage. Vasopressin may be effective in raising MAP in patients with refractory hypotension; however, the optimal time to initiate this drug is not clear. A meta-analysis that included results of the Vasopressin and Septic Shock Trial (VASST) showed reduced noradrenaline requirements in patients with septic shock but no significant survival benefit in the short term [13, 14].

Oxygen-Carrying Capacity

Liberal transfusion to a haemoglobin value of >10 g/dL has been promoted as part of the early goal-directed therapy (EGDT) to augment oxygen-caring capacity and oxygen delivery to the tissues, especially if venous O_2 saturation targets are not achieved ($SpvO_2$ <70 %) during the first 6 h of resuscitation [1]. This hypothesis was not confirmed in the recent Transfusion Requirements in Septic Shock (TRISS) trial [15]. In this trial patients with septic shock were randomised to receive transfusion at a haemoglobin threshold of either 7 g/dL or 9 g/dL. The restrictive approach

resulted in about half the amount of transfusion requirements without a significant difference in the mortality at 90 days or the rate of ischaemic events and use of life support. TRISS did not specifically address the role of blood transfusion as part of a resuscitation strategy in the first 6 h but insights gained from two early goal-directed resuscitation trials, [3, 4] which did not demonstrate a difference in overall mortality, make it likely that a restrictive transfusion strategy is the better option for septic patients.

In the absence of a demonstrable benefit from the use of a liberal transfusion strategy, a restrictive transfusion threshold with a transfusion trigger of haemoglobin of 7.0 g/dL is advocated. A higher haemoglobin level may be necessary in special circumstances such as acute coronary syndrome, life-threatening bleeding or acute burn injury.

Treatment of Infection

Along with adequate resuscitation, appropriate initial antimicrobial therapy is the critical determinant of survival in sepsis and septic shock. Beyond the issues related to infecting organisms and their sensitivity profile, optimal antimicrobial therapy in the critically ill includes consideration of host factors, site of infection and altered pharmacokinetics. In many circumstances, standard regimens require modification.

Appropriate Antimicrobial Therapy

The correct choice of antibiotics has consistently been associated with improved outcomes from septic shock. The empirical choice of therapy is determined amongst others by a number of variables including the site of infection, commonly encountered microbes and local antibiotic susceptibility patterns. Empirical coverage should include broad-spectrum antibiotics or a combination, which has Gram-negative aerobic and Gram-positive activity. Emergence of antimicrobial resistance, and occurrence of infection with nonbacterial pathogens, contributes to the increasing rates of treatment. Risk factors for infection with resistant organisms include prolonged hospital stay, residence in a long-term healthcare facility, prior colonisation or infection with multidrug-resistant organisms (MRO).

Timeliness of Antimicrobial Therapy

In their landmark study, Kumar et al. [16] showed that for every hour of delay in initiating appropriate antibiotic therapy for patients presenting with septic shock (from the onset of hypotension), there was an associated 8 % increase in mortality. A retrospective analysis of a large dataset from 28,150 patients with severe sepsis

and septic shock admitted to ICUs in Europe, the United States and South America demonstrated that each hour delay in antibiotic administration was associated with a linear increase of in-hospital mortality across all areas in the hospital and regardless of the level of illness severity [17].

Intravenous antibiotic therapy should therefore be started as early as possible, preferably within the first hour of recognition of severe sepsis. Any delay is likely to negatively impact on chances of survival.

Source Control

Appropriate and early source control reduces the load with infective pathogens. Accordingly, septic patients should be rapidly evaluated with integration of clinical history, physical examination, focused diagnostic tests and imaging for a possible source of infection resuscitation, infectious foci should be controlled as soon as possible with the least physiological insult possible (e.g. percutaneous and endoscopic versus surgical approach). Intravascular catheters or indwelling devices that are potential source of sepsis should be promptly recognised and removed. Early surgical intervention has been shown to have a significant impact on outcome in certain rapidly progressive infections such as necrotising fasciitis.

Supportive Care

Mechanical Ventilation

Lung-protective ventilation is an important aspect of management as sepsis is often complicated by acute lung injury. It consists of ventilating patients with tidal volumes of 6 ml/kg predicted body weight, trying to keep the airway plateau pressure below 30 cm H_2O and permitting a moderate grade of hypercapnia to reach this goal [18]. Positive end-expiratory pressure should be set to avoid lung alveolar collapse at end expiration.

Renal Replacement Therapy

Renal dysfunction in sepsis can be profound and may contribute to significant morbidity and mortality. Renal replacement therapy is the mainstay of supportive treatment of patients with severe acute kidney injury. Beyond this, it has been postulated that removing inflammatory molecules with continuous renal replacement therapy (CRRT) may be advantageous in sepsis. However, this hypothesis could not be confirmed in the pre-specified subgroup of septic patients in two large multicentre, randomised trials designed to assess two levels of intensity of renal replacement therapy in critically ill patients with acute kidney injury [19, 20].

Adjuvant Therapy

Steroids

Dysfunction of the hypothalamic-pituitary-adrenal axis in sepsis, which has been termed critical illness-related corticosteroid insufficiency, is a syndrome where the magnitude of adrenal response does not match the degree of stress. A meta-analysis of randomised controlled studies of low-dose hydrocortisone in patients with septic shock demonstrated earlier shock reversal but came to conflicting conclusions regarding survival of patients [21]. At the time of writing, the multicentre, double-blind, placebo-controlled ADRENAL (ADjunctive coRticosteroid trEatment iN criticAlly ilL patients with septic shock) trial is randomising patients to determine whether hydrocortisone therapy reduces 90-day all-cause mortality of patients with septic shock [22].

Prognosis

Since the early 1990s, mortality rates of patients with severe sepsis enrolled in usual care arms of multicentre randomised trials and large retrospective, observational studies have steadily declined [23, 24]. The observed decrease in mortality over the past decade has occurred in the absence of novel therapeutic advances and is likely due to improved processes of care in the emergency department and the ICU. This has led to the use of sepsis care bundles, which on before-after studies have reported reductions in mortality, apparently justifying bundle validity and calling for widespread adoption. Several observational studies have demonstrated that patients with severe sepsis treated in hospitals with higher case volumes have lower case fatality rates. On the other hand, some studies provide compelling evidence to question the concept of bundling by pointing out that individual elements of these bundles other than timely administration of antibiotics do not improve patient outcome.

Despite optimal care, approximately 20–30 % of patients with severe sepsis and 30–40 % with septic shock do not survive hospitalisation. Those who die in the early stages do so of refractory hypotension and overwhelming multi-organ failure. Death later in the course of illness occurs as a result of nosocomial infections and complications of the underlying disease.

Conclusion

Severe sepsis is a condition as common as acute myocardial infarction and like coronary artery disease, it is a major source of short-term and long-term morbidity and mortality. Aggressive management of haemodynamic changes associated with

sepsis and early appropriate antibiotic therapy improve outcomes. It is likely that the greatest opportunity to improve patient outcome comes not from discovering new treatments but from more effective delivery of existing best practice therapies.

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