A vigorous immune response is vital to localise, contain and eliminate infection. However, this response can have systemic complications, leading to the clinical presentation of sepsis, septic shock, organ failure and death.

Nomenclature and definitions

Although severe sepsis is a relatively recent concept, the association of disseminated or localised infection with circulatory collapse and death has been recognised for many years. The term 'sepsis' describes the physiological response to infection (Table 1), but is often loosely applied to any manifestation of infection and, on its own, has little meaning. Septicaemia has traditionally been used to describe the association of bloodstream invasion (bacteraemia) with severe systemic illness, but it is a relatively imprecise term. Furthermore, some non-infective conditions, such as pancreatitis or severe trauma, can give rise to a similar clinical and physiological picture. Thus, a debate started in the late 1980s to generate a consensus to aid both clinical diagnosis and research. This created the concept of a continuum of pathophysiological responses (as outlined in Table 1). Severe sepsis can then be identified as the clinical syndrome in patients who are developing organ dysfunction as a result of the systemic response to infection.

The advantage of such a scheme is that it provides a relatively precise definition of terms, allowing comparison of clinical and research data. It has, however, been criticised because sepsis is a heterogeneous condition, and lumping everything together tends to imply uniform pathogenesis, disease manifestations and therapy. Currently, there is no classification that will satisfy everyone, but the definitions in Table 1 can be used both as a basis for identifying patients at risk of developing organ failure associated with severe sepsis and for targeting therapeutic intervention to this patient group.

Epidemiology

The true incidence of severe sepsis is not known. Sepsis is a heterogeneous condition, with varying rates in different patient populations. Furthermore, it is not a notifiable disease and differences in definitions and diagnostic methods make comparisons between different patient populations difficult.

Nevertheless, however defined or diagnosed, severe sepsis is a major cause of morbidity and mortality. In the UK, community-acquired bacteraemia is responsible for approximately 7–12 per 1,000 hospital admissions, and in a proportion of patients will be associated with sepsis and shock. Kieft et al recorded severe sepsis in 13.6 per 1,000 and septic shock in 4.6 per 1,000 hospital admissions to a large Dutch teaching hospital. In the USA, the annual incidence of sepsis is of the order of 400,000 cases per year, with 200,000 cases of septic shock and an estimated 100,000 deaths. In addition, the prevalence of severe sepsis within hospital has been increasing over the past 30 years, presumably due to greater numbers of critically ill patients at risk of hospital-acquired infection.

The prevalence of infection and sepsis is particularly high in the intensive care unit (ICU). The European Prevalence of Infection in Intensive Care (EPIC) study revealed a point prevalence of 44.8% infection in European ICUs. In a prospective study, 68% of 3,708 patients fulfilled the criteria for the systemic inflammatory response syndrome (SIRS) at some time during...
their ICU stay\textsuperscript{10}. This latter study clearly documented for the first time the transition of some patients from sepsis through severe sepsis to multi-organ failure over a period of hours to days, thus highlighting the potential for therapeutic intervention.

Mortality is estimated at 10–20\% for bacteraemic patients, 20–30\% for bacteraemia plus sepsis, 40–60\% in severe sepsis, and over 80\% in multi-organ failure. Data from trials of novel therapeutic agents in severe sepsis revealed 14-day and 28-day mortalities of 26\% and 42\%, respectively\textsuperscript{11}, but these studies excluded the most severely ill patients. Also, many patients have serious comorbidities, which are closely linked to outcome\textsuperscript{2}. Survivors of severe sepsis demonstrate a continuing above average mortality for at least five years following the acute event\textsuperscript{7}.

Risk factors
All infections are the result of a complex interaction between the host (immune response) and the environment (exposure to pathogens). In immunocompetent individuals without any underlying disease focus, severe sepsis will generally be due to highly pathogenic organisms such as \textit{Neisseria meningitidis} or beta-haemolytic streptococci. In an immunocompromised hospital population, however, less pathogenic or opportunistic infections will be encountered. Many different host and environmental factors combine to place an individual at risk of sepsis (Fig 1).

Microbiology
Bacterial species are the commonest aetiological agents of both community-acquired\textsuperscript{12} and hospital-related sepsis\textsuperscript{13} (Table 2\textsuperscript{14,15}). Gram-negative bacteria were closely associated with septic shock in the 1960–70s\textsuperscript{16}, but more recently there has been an increase in the proportion of cases related to Gram-positive infection\textsuperscript{8,11}. In addition, there has been a rise in multiply resistant bacteria such as \textit{Acinetobacter} spp, enterococci and methicillin-resistant

<table>
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<tr>
<th>Infection</th>
<th>Invasion of microorganisms into a normally sterile site, often associated with an inflammatory host response</th>
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<tr>
<td>Bacteraemia</td>
<td>Viable bacteria in bloodstream</td>
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<tr>
<td>Septicaemia</td>
<td>No uniform definition, often interpreted as bacteraemia plus severe illness</td>
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<tr>
<td>Sepsis</td>
<td>Clinical evidence of infection plus systemic response indicated by two or more of: hyper- or hypothermia: core temperature &gt;38°C or &lt;36°C; tachycardia: heart rate &gt;90 bpm; tachypnoea: respiratory rate &gt;20 resp/min; WBC &gt;12 x 10(^9) or &lt;4 x 10(^9) or ‘left shift’</td>
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| Severe sepsis | Sepsis associated with organ dysfunction: hypotension; oliguria; hypoxia; confusion; metabolic acidosis; DIC |

| Septic shock | Severe sepsis with hypotension unresponsive to intravascular volume replacement |

| Refractory shock | Hypotension not responding to vasoactive agents |

| SIRS | Similar physiological response to sepsis but unrelated to infection May be caused by a variety of acute insults (eg pancreatitis) |

DIC = disseminated intravascular coagulation; SIRS = systemic inflammatory response syndrome; WBC = white blood cell.

Table 1. Working definitions for conditions related to sepsis (adapted from Ref 3).

Fig 1. Interaction of host and environmental factors that may place an individual at risk of infection and sepsis (ICU = intensive care unit).
Staphylococcus aureus, and more cases related to fungal infection. These changes in bacteriology are presumably related to increased use of long-term intravenous lines, hospital antibiotic use, more immunocompromised patients, and the prolonged survival of critically ill patients in the ICU. Sepsis related to Pseudomonas aeruginosa, mixed bacterial infection or candidiasis is associated with higher mortality than other pathogens.

Less commonly, non-bacterial micro-organisms, including fungi, protozoa (malaria), rickettsiae (Rocky Mountain spotted fever) and viruses (viral haemorrhagic fevers), may be associated with sepsis and shock.

**Clinical features**

Septic shock is a medical emergency. Full assessment may need to wait until resuscitation and empiric antimicrobial therapy have been commenced.

When assessing a patient with suspected sepsis, try to answer the following questions:

- Is the patient infected?
- What is the site of infection?
- What is/are the likely infecting organism(s)?
- Is the patient shocked or developing organ failure?

Sepsis has many common features in different types of infection, but the site of infection, microbiology and host response will influence the exact clinical picture. Severe sepsis may be difficult to spot when the response to infection is impaired. Thus, a high index of suspicion should be maintained in the elderly or immunocompromised, and underlying sepsis should be considered in the differential diagnosis of any unexplained deterioration in organ function.

**History**

The history is vital, but may be difficult to obtain from critically ill patients. As much collateral information as possible should be sought. In taking the history, an attempt is being made to identify factors for acquiring infection (Fig 1), clues to the infected site, and information to guide empiric antimicrobial therapy. Ask about symptoms, underlying immunosuppressive illness or medication, previous hospitalisation, recent surgical procedures, indwelling prosthetic devices, prior antibiotics, local outbreaks, contact with animals, and recent travel.

A good example is that of a previously well individual presenting with a rapidly progressive illness characterised by fever, hypotension, headache and confusion. In the UK, the differential diagnosis includes any community-acquired bacteraemia or meningoencephalitis. However, if the patient has just arrived back from Africa, malaria, typhoid, trypanosomiasis and viral haemorrhagic fevers would also need to be considered.

General symptoms associated with sepsis include sweats, chills or rigors, breathlessness, diarrhoea, nausea and vomiting, myalgia, and headache. Ask about specific symptoms to localise the infected site, including cough/sputum production, dysuria, abdominal pain or meningism – but in many cases there are no clues. Confusion is present in 10–30% of patients, especially the elderly, and does not necessarily imply central nervous system infection. Do not forget that diarrhoea and breathlessness are common non-specific features of severe sepsis, and do not simply conclude that the patient has gastroenteritis.

**Examination**

'Sepsis' refers to the physiological response to infection but, with progression to severe sepsis and shock, organ dysfunction will become increasingly apparent. Remember that sepsis is a dynamic process, with the rapid evolution of physical signs over minutes to hours. Frequent evaluation and careful monitoring of patients are essential, particularly when there is doubt over the diagnosis, as in early meningococcal sepsis.

Patients with severe sepsis are typically febrile, tachypnoeic, hypotensive and tachycardic, with warm peripheries and a bounding arterial pulse. In addition, they may be oliguric, jaundiced or disoriented (Table 3). However, many patients have a more subtle presentation, and a high index of suspicion is required to recognise early disease. Fever may be absent, particularly in the elderly, and severe cases may present with hypothermia. Although one of the characteristic features of sepsis is peripheral vasodilatation, patients can sometimes...
present with cool peripheries due to cardiovascular collapse, and may be misdiagnosed as cardiogenic shock. Severe sepsis must be considered in the differential diagnosis of any patient presenting with unexplained hypotension. Conversely, even in a patient who is clearly infected, other causes of shock such as myocardial infarction, cardiac tamponade or hypovolaemia must be considered. Hypotension in sepsis is often multifactorial, and sepsis may complicate or co-exist with other causes of shock.

Detailed and complete physical examination is essential. The skin, all wounds, conjunctivae and fundi must be examined, and a full ear, nose and throat examination performed as these sites are often overlooked (Fig 2). Classic clues include:

- the petechial/purpuric rash or peripheral gangrene of meningococcaemia
- peripheral emboli in endocarditis
- cellulitis or necrotising fasciitis around a wound
- erythematous rash or desquamation in staphylococcal or streptococcal toxic shock
- the retinal lesions of candida endophthalmitis.

Focal signs of infection such as pneumonia or pyelonephritis should be sought. Rectal and vaginal examination may also reveal valuable clues as to the diagnosis, and should be performed when indicated. For example, retained tampons are implicated in the pathogenesis of staphylococcal toxic shock in menstruating women.

The examination may reveal the focus of infection, but often it is still unclear at the time of presentation.

Where sepsis develops in hospital, particular attention should be paid to indwelling intravenous/intra-arterial lines. If the entry site of the line is inflamed or leaking pus, it is likely to be the source of infection and should be removed as soon as possible. Insist on exposing and examining all wounds (Fig 3), and carefully review the pressure areas as these are frequently neglected sources of infection.

Investigations

Specific investigations are used to try to identify the site/nature of the underlying infection or to recognise the development and progress of severe sepsis. The main systemic abnormalities in severe sepsis are summarised in Table 3.

Microbiological studies

(Microbiological studies will be discussed in detail in a later article in this series.) The microbiological investigation of sepsis often conflicts with clinical management. Where shock or organ failure is present, or the patient appears at high risk of either or both of these, early empiric antibiotic therapy may be life saving. Therefore, once a

![Fig 2. A patient who presented with fever, hypotension and decreased consciousness. Conjunctival petechiae were secondary to Staphylococcus aureus endocarditis. Septicaemia due to Neisseria meningitidis can also cause conjunctival petechiae.](image1)

![Fig 3. An elderly woman who presented with a low-grade fever and confusion. No cause was apparent until the bandages covering her chronic venous leg ulcer were removed revealing cellulitis, in this case due to beta-haemolytic Streptococcus pyogenes.](image2)
clinical diagnosis has been made, antibiotics should not be delayed simply in order to obtain good cultures. Conversely, every effort must be made to secure as much material for culture as possible. In the community, empiric antibiotics should be started immediately in suspected meningococcal septicaemia, but in hospital it should always be possible to take blood for culture while the antibiotics are being prepared.

In taking blood cultures, an inadequate volume of blood is the most common reason for not detecting bacteraemia. A total of 20–30 ml of blood should be inoculated into one of the standard commercial blood culture media (2 or 3 sets). In addition, sputum and urine should be obtained for microscopy and culture, all wounds swabbed and drained, and any abscesses cultured. Sterile body sites such as cerebrospinal fluid, joint or pleural fluid, should be sampled as clinically indicated. Do not forget that patients with severe sepsis/septic shock are at a higher risk of acquiring further infections, so cultures should be repeated as directed by the condition of the patient.

<table>
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<tr>
<th>Table 3: Key systemic features of severe sepsis.</th>
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<tbody>
<tr>
<td><strong>Temperature</strong></td>
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<td><strong>Pulse</strong></td>
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<td><strong>Blood pressure</strong></td>
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<td><strong>Haemodynamics</strong></td>
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<td><strong>Respiration</strong></td>
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<td><strong>Metabolic</strong></td>
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<td><strong>Renal</strong></td>
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<td><strong>Neurology</strong></td>
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ARDS = acute respiratory distress syndrome; BP = blood pressure; DIC = disseminated intravascular coagulation; WBC = white blood cell.

Haematology

Sepsis is most commonly bacterial in origin and associated with a neutrophil leucocytosis. Review of the blood film may show toxic granulation of neutrophils when the white cell count remains within the normal range. Leukopenia in sepsis is associated with a poor prognosis. Thrombocytopenia suggests disseminated intravascular coagulation (DIC), and evidence of haemolysis may be visible on a blood film. Prolonged prothrombin or activated partial thromboplastin time, low fibrinogen and elevated markers of fibrinolysis also indicate DIC.

Biochemistry

It is essential to monitor renal function closely. Hyponatraemia at presentation is a poor prognostic sign and an elevated potassium may indicate rhabdomyolysis. Amylase, creatinine kinase, calcium and magnesium levels should be measured at baseline. Hypoglycaemia may occur in severe sepsis.

Metabolic acidosis is one of the most frequent abnormalities in severe sepsis and must be monitored in all cases. Plasma lactate is often increased 3–5 fold in the sepsis syndrome (normal 1–2.5 mmol/l) and relates to the degree of tissue hypoxia. In early sepsis, arterial blood gases often show a normal oxygen saturation and a respiratory alkalosis to compensate for increased lactate production. As organ failure progresses, arterial pH starts to fall, and the onset of significant hypoxia indicates severe disease and a high risk of the acute respiratory distress syndrome (ARDS).

Minor liver function abnormalities are common in patients with bacteremia and sepsis. However, an elevated bilirubin or an obstructive pattern of liver derived enzymes can indicate a biliary source of infection and should be investigated appropriately. In a patient with established severe sepsis, worsening liver function suggests the complication of acalculous cholecystitis. Serum albumin may fall rapidly in severe sepsis.

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<th>Table 4: Haemodynamic changes during sepsis.</th>
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<td><strong>Heart rate</strong></td>
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<td><strong>Mean arterial pressure</strong></td>
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<td><strong>Central venous pressure</strong></td>
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<td><strong>Pulmonary capillary wedge pressure</strong></td>
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<td><strong>Cardiac output</strong></td>
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<td><strong>Systemic vascular resistance</strong></td>
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<td><strong>Oxygen delivery</strong></td>
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as a consequence of widespread endothelial damage and capillary leak.

C-reactive protein (CRP) is an acute-phase reactant that rises within a few hours of the onset of bacterial infection. However, it is important to remember that in fulminant infective shock, for example meningococcal septicemia, CRP may be normal at initial presentation. In addition, CRP does not reliably distinguish septic from non-septic causes of shock. Sequential CRP measurements may be useful in monitoring the response to therapy.

**Haemodynamic monitoring**

Sepsis is associated with a range of physiological changes (Table 4). Measurement of these variables by invasive or non-invasive monitoring may aid diagnosis and management. (This will is discussed in more detail in a later article in the series.)

**Radiology**

Sophisticated imaging techniques have allowed more accurate imaging of hidden infective foci: for example, deep-seated abscesses. A chest X-ray must be performed in all patients at presentation, both to detect a potential pulmonary source of infection and for early signs of ARDS. Ultrasound and computed tomography are particularly useful when trying to detect deep abscesses, and in selected cases nuclear medicine techniques may pinpoint the site of infection. Once a focus has been identified, the skills of the interventional radiologist become invaluable both in establishing a diagnosis and in therapy.

**Prospects for the future**

Improved management of patients with sepsis in the future will depend on the development of tests which will rapidly diagnose specific infections and predict which patients are likely to develop organ failure. The emergence of DNA-based technology is likely to aid the rapid diagnosis of some infections. A high sensitivity and specificity polymerase chain reaction-based test for *N. meningitidis* is already in clinical use, although it is being used mainly for epidemiological purposes. Measurement of plasma endotoxin or inflammatory mediators such as interleukin-6 has been evaluated in research studies. Although the studies have been promising, to date these tests are not sufficiently accurate to predict outcome to be useful in the management of individual patients.

**Conclusion**

Severe sepsis/septic shock is a severe complication of disseminated or localised infection that can lead to organ failure and death. Any organ system may be affected, and prompt recognition of the early signs associated with sepsis is essential to prevent disease progression.

**References**


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