Sepsis

Andrew J Brent

Abstract

Sepsis occurs when a dysregulated host response to infection causes potentially life-threatening organ dysfunction. It is usually caused by bacterial infection and carries a 30% mortality, causing millions of deaths worldwide each year. New definitions have recently been published for clinical practice and research. Effective management requires prompt recognition, antimicrobial therapy, source control and supportive treatment. Early, appropriate antimicrobial therapy is associated with improved survival from sepsis. Rapid identification and control of the source of infection (e.g. drainage of pus) is equally important in many cases. These and other elements of the initial management of sepsis are incorporated into the 'Sepsis Six' bundle of care.

Keywords Antibiotics; antimicrobial therapy; infection; MRCP; sepsis; septic shock

Key points

- Sepsis occurs when a dysregulated host response to infection causes potentially life-threatening organ dysfunction with a mortality of approximately 30%
- Early recognition and treatment of sepsis saves lives
- Management includes antimicrobial therapy, source control and supportive care

Definitions

Sepsis describes a syndrome of life-threatening organ dysfunction caused by a dysregulated host response to infection. It is usually caused by bacterial infection. Various definitions have been proposed for both clinical practice and research. The previous definition of a systemic inflammatory response syndrome (SIRS) to infection was poorly discriminative. Two new definitions were published in 2016 as part of management guidelines from an international critical care task force (Sepsis-3)[1] and the UK National Institute for Health and Care Excellence (NICE)[2] — see below.

Epidemiology

Sepsis has a mortality of approximately 30%, causing around 5 million deaths worldwide and >40,000 deaths in the UK annually. Common presenting syndromes include pneumonia, intra-abdominal and urinary sepsis, and skin and soft tissue infections. Causative agents depend on the syndrome, host and clinical context. Gram-negative infections account for an increasingly large proportion of cases, particularly of healthcare-associated infections.[3] Risk factors for infection are summarized in Table 1.

Pathophysiology

Highly conserved microbial structures, like lipopolysaccharide (endotoxin) in Gram-negative bacteria, trigger pattern recognition receptors (e.g. Toll-like receptors) causing a cytokine cascade, leucocyte, complement and coagulation activation, and vascular endothelial dysfunction.[3] Microvascular thrombosis caused by dysregulated coagulation, combined with vasodilatation and hypotension, causes tissue hypoperfusion, and oxidative stress worsens mitochondrial dysfunction.

The downstream effect of this proinflammatory response is impaired tissue oxygenation. The resulting tissue injury releases endogenous proinflammatory molecules that perpetuate the inflammatory response and organ dysfunction. Compensatory anti-inflammatory mechanisms increase vulnerability to secondary infections. The balance between pro- and anti-inflammatory effects and the resulting clinical phenotype vary during an episode and between patients.

Clinical presentation

Clinical features of sepsis are related to the systemic inflammatory response, the infection focus and organ dysfunction (Table 2).[3] Symptoms and signs vary considerably and can be subtle, particularly in young children and elderly or immunocompromised individuals.

Septic shock occurs when severe sepsis leads to circulatory failure and metabolic abnormalities, defined as persisting hypotension requiring vasopressors to maintain mean arterial pressure ≥65 mmHg and serum lactate concentration >2 mmol/litre despite adequate fluid resuscitation. It carries a mortality of ≥40%.[1]

Screening and diagnosis

Screening for sepsis is now routine in many settings. However, there is no consensus on the best screening approach.

The ***Sepsis-3 guidelines***[1] advocate two-stage screening of adults with suspected infection to identify those at highest risk of poor outcome. Sepsis is defined as the presence of ≥2 'quick SOFA (qSOFA)' parameters (respiratory rate >22/minute, altered mentation, systolic blood pressure <100 mmHg) plus an increase of ≥2 in the Sequential Organ Failure Assessment (SOFA) score.

The ***2016 NICE Sepsis guidelines***[2] risk-stratify adult and paediatric patients with suspected infection according to the presence of 'high-risk' (Table 2) and 'moderate-to-high-risk' criteria. These are incorporated into age- and setting-dependent algorithms dictating further investigation and treatment. However, their complexity has attracted criticism, and high-quality evidence to justify much of the complexity is lacking.

Several large studies have demonstrated the superiority of Sepsis-3 over the old SIRS criteria for predicting adverse outcome

Andrew J Brent *MRCP PhD DTM&H is a Consultant and Honorary Senior Clinical Lecturer in Infectious Diseases at Oxford University Hospitals Foundation Trust and the University of Oxford, UK.*
Competing interests: none declared.

Please cite this article in press as: Brent AJ, Sepsis, Medicine (2017), http://dx.doi.org/10.1016/j.mpmed.2017.07.010

Risk factors for sepsis

Increased risk of infection	• Environmental factors (hygiene, sanitation)
	• Susceptibility of individual organs to infection, e.g.:
	  ○ Chronic obstructive pulmonary disease, bronchiectasis — respiratory infections
	  ○ Lymphoedema, ulcers, psoriasis, etc. — skin infections
	  ○ Urethral catheter — urinary tract infections

Impaired immune response	• Congenital immunodeficiency syndromes • HIV/AIDS • Neutropenia • Splenectomy/hyposplenism • Iatrogenic (corticosteroids, chemotherapy, biological agents) • Other chronic conditions (e.g. malnutrition, diabetes mellitus, malignancy)
Pre-existing organ dysfunction	• Increased risk of organ failure from reduced physiological reserve, e.g. heart failure, chronic respiratory disease, chronic kidney disease
Extremes of age	• Neonates and infants (immature immunity, limited physiological reserve) • Elderly patients (immune senescence, co-morbidity)
Other genetic factors	• Ethnicity (incidence higher among some racial groups) • Sex (incidence higher among male patients) • Specific immune defects, e.g. defect in terminal complement pathway leading to increased risk of meningococcal sepsis
Infection management	• Delayed or inappropriate initial treatment of bacterial infections increases risk of progression to sepsis

Table 1

and death among adult inpatients with suspected infection. The limited data available to date suggest that the NICE criteria are less discriminating. Interestingly, in a recent large study, the ***National Early Warning Score (NEWS)*** was more discriminating than SIRS or qSOFA among >30,000 adult inpatients.[4] Using a generic early warning score to identify the sickest patients is attractive because early warning scores are already embedded in clinical practice, and sepsis is only one (albeit important) cause of clinical deterioration. Sepsis may be incorporated into NEWS2, to be published later this year.

The best approach to sepsis screening among children, pregnant women and non-hospital settings is even less clear. Identifying sepsis in children is particularly challenging because viral infections that do not require antimicrobial therapy represent a large proportion of the presenting caseload. Early data suggest poor specificity of the NICE algorithms, and a number of different paediatric early warning scores and alternative screening tools are used.

Management

The key principles of management are prompt recognition, early appropriate antimicrobial therapy, source control, supportive treatment and antimicrobial stewardship (Table 3). Elements of the initial management of sepsis are incorporated into the Sepsis Six bundle of care.

Rapid clinical assessment is indicated for all patients with suspected sepsis. As for other medical emergencies, use an 'assess and treat' approach to quickly establish the key elements of the history and examination, and — if the working diagnosis of sepsis is confirmed — start treatment. Rapid delivery of a bundle of care comprising elements of the Sepsis Six (Table 3) has been associated with reduced mortality in sepsis.[5]

Investigations aim to confirm the presence, source and severity of infections and alternative diagnoses (Table 3). Where possible, it is important to obtain samples for microbiology before administering antibiotics to maximize culture sensitivity. Except in exceptional circumstances, at least one set of blood cultures should be obtained. The timing of other cultures (e.g. urine, cerebrospinal fluid, repeat blood cultures for suspected endocarditis) depends on the clinical presentation, illness severity and likely delay in obtaining a sample; in general, however, antibiotics should not be delayed in true sepsis. If in doubt, discuss the patient urgently with a senior or infection specialist.

Antimicrobial therapy should be administered as rapidly as possible in sepsis, and within 1 hour, as early appropriate antibiotics are associated with improved survival.[3] The choice of initial empirical antibiotic therapy depends on the presenting clinical syndrome (including likely focus of infection, neutropenia, etc.) and should follow local guidelines based on the most likely pathogens and susceptibility profiles. The need, route of administration and choice of antibiotics should be reviewed daily in light of clinical progress and investigations.

Source control is equally crucial to the management of many focal infections and should be performed as rapidly as possible. It includes removal of infected lines/devices, drainage of collections, nephrostomy insertion for an infected-obstructed renal system, washout of infected joints, etc. Although some patients may first need to be stabilized, source control is in some cases (e.g. necrotizing fasciitis) just as or more important than antimicrobial therapy.

Supportive treatment includes oxygen to treat hypoxia and ensure good tissue oxygenation, and intravenous fluids to optimize tissue perfusion. Vasopressors and inotropes may be required in septic shock, mechanical ventilation for severe pneumonia or acute respiratory distress syndrome, and renal replacement therapy for acute kidney injury. Patients who

Please cite this article in press as: Brent AJ, Sepsis, Medicine (2017), http://dx.doi.org/10.1016/j.mpmed.2017.07.010