Sepsis is a potentially life-threatening condition and therefore a medical emergency. Sepsis may not be obvious and a high index of suspicion is often required to make the diagnosis. Early aggressive treatment increases the chance of survival and every hour that treatment is delayed increases mortality[1].

Sepsis is defined as life-threatening organ dysfunction due to a dysregulated host response to infection[2].

Septic shock is associated with particularly profound circulatory, cellular and metabolic abnormalities, with a greater risk of mortality than with sepsis alone. Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and serum lactate level greater than 2 mmol/L in the absence of hypovolaemia. This combination is associated with hospital mortality rates greater than 40%[3].

The Surviving Sepsis Campaign (SSC) was established to raise awareness of severe sepsis and to improve its management[4]. The SSC is a collaboration between several groups worldwide and its aim is to reduce the mortality from sepsis.

Pathophysiology of sepsis[5]

The hallmark of sepsis is derangement in physiology. This may include:

- Abnormal coagulation.
- Endothelial cell dysfunction[6].
- Presence of excessive tumour necrosis factor.
- Cell apoptosis - eg, lymphocytes and endothelial cells.
- Neutrophil hyperactivity.
- Poor glycaemic control.
- Lack of steroid hormones.
- Cytokines, proteases, lipid mediators, gaseous substances, vasoactive peptides and cell stress markers play key roles in sepsis pathophysiology[7].
- Current research is focusing on such issues as the immunosuppressive phase of host immune responses, mitochondrial dysfunction and the individual reactions between pathogen and the host immune system[8].

Epidemiology

Sepsis is the most common cause of death among critically ill patients in non-coronary intensive care units[9].

Lack of reliable epidemiological data makes global estimates difficult. However, it has been deduced that more than 1 in 1,000 people in developed countries develop sepsis each year and between a third and a half of them progress to severe sepsis. The figures for developing countries are likely to be far higher[10].

Risk factors[9]

There is usually an abscess or nidus of infection, which may be occult. Risk factors for developing sepsis include the following:

- Age - the elderly (over 75 years) and very young (< 1 year) are at risk.
- Instrumentation or surgery (including illegal abortion occurring in unhygienic circumstances).
- Indwelling line or catheter.
- Alcohol abuse.
- Diabetes mellitus.
- Breach of skin integrity eg, burns.
- Immunocompromise.
- Medications - eg, high-dose corticosteroids, chemotherapy.
- Males are more prone than females to develop severe sepsis, although the mortality in females is higher. The reasons for this are not known[11].
- Intravenous drug misuse.
- Pregnancy.

Presentation[12]

Early recognition is essential. Presenting features may be nonspecific and vague. A high degree of vigilance is therefore required at all times.
Patients may have presented a few days earlier with a focus of infection.
Patients may then deteriorate rapidly despite having the appropriate oral antibiotics.
Non-specific symptoms are common - eg, lethargy, nausea and vomiting, abdominal pain and diarrhoea.
Also enquire about symptoms relating to a possible focus of infection - eg, cough, urinary symptoms, recent travel.
Ask about frequency of micturition in the past 18 hours.
Presenting features for children may include feeling abnormally cold to touch, looking mottled and blue or with very pale skin, a rash that does not fade with pressure, raised respiratory rate and being very lethargic and difficult to wake up.
Young children may not feed, may have repeated vomiting or may not pass any urine and so not have wet nappies.

A high degree of vigilance is required for early identification of a patient with sepsis in primary care. It is particularly recommended to assess any patient for sepsis who:

- Has clinical evidence of systemic infection (such as recent history of fever).
- Is considered for antibiotic treatment.
- Is suspected of having influenza.
- Is suspected to have gastroenteritis.
- Is obviously unwell without clear cause.
- Has altered mental state or behaviour.
- Is elderly or immunosuppressed and presents with signs of infection.
- Has deteriorated on antibiotic therapy.

Sepsis screening

Systolic blood pressure <90 mm Hg (or >40 mm Hg fall from baseline).
Heart rate >130 beats per minute.
Oxygen saturations <91%.
Respiratory rate >25 breaths per minute.
Responds only to voice or pain/unresponsive.
Lactate >2.0 mmol.

Immediate action is indicated if ANY ONE of those criteria is present. The values provided are only a guide and the observations should be interpreted in context. For example a blood pressure of 105/60 mm Hg for an older person is likely to be much lower than their baseline but may be normal for a fit young adult.
An alternative is the National Early Warning System introduced by the Royal College of Physicians in 2012[15]. This is based on a simple scoring system in which a score is allocated to physiological measurements already undertaken when patients present to, or are being monitored in hospital. Six simple physiological parameters form the basis of the scoring system:

1. Respiratory rate
2. Oxygen saturations
3. Temperature
4. Systolic blood pressure
5. Pulse rate
6. Level of consciousness

A score is allocated to each as they are measured, the magnitude of the score reflecting how extremely the parameter varies from the norm. The score is then aggregated. The score is uplifted for people requiring oxygen. It is important to emphasise that these parameters are already routinely measured in hospitals and recorded on the clinical chart. This system is also recommended by NICE guidance (2016)[16].

**NB:** In children (those aged <12 years) assess temperature, heart rate, respiratory rate, level of consciousness, oxygen saturation and capillary refill time. If there is a correct size blood pressure cuff for the child's age, measure the blood pressure. Women who are pregnant should NOT be assessed with this system because the physiological response to acute illness can be modified in pregnancy.

**Investigations**[17, 18]

**These should include:**

- FBC - anaemia, neutrophilia or neutropenia, thrombocytopenia may be present (pancytopenia may indicate bone marrow involvement). In viral infections lymphocytosis predominates.
- Urine dipstick and sample for microscopy, culture and sensitivity.
- Renal function - looking at extent of dehydration or organ failure.
- LFTs - hypoalbuminaemia likely to be present.
- Glucose - hyperglycaemia can be present.
- Clotting screen, including D-dimer and fibrinogen testing, looking for disseminated intravascular coagulation.
- Blood cultures - at least two are required. Cultures for mycobacteria should also be sent. Ideally these should be sent before antibiotics are given - but do not delay, especially if the patient is very ill.
- Radiology - including CXR, abdominal ultrasound looking for a collection, and CT scan looking for source.
- Measures of lactate and oxygen saturation of venous blood (SvO₂).
- Arterial blood gases - metabolic acidosis is common.
- More invasive investigations looking for a source of infection - for example, lumbar puncture, bronchoscopy, laparoscopy, lymph node biopsy, etc.

**Complications**

- Disseminated intravascular coagulation.
- Adrenal failure - eg, adrenal haemorrhage secondary to meningococcus (Waterhouse-Friderichsen syndrome).
- Multiorgan failure - eg, renal failure or cardiorespiratory failure.
Management

The key immediate interventions that are associated with significant mortality reductions when applied within the first hour are:\[19\]:

- Administer high-flow oxygen.
- Take blood cultures and consider infective source.
- Administer intravenous antibiotics.
- Give intravenous fluid resuscitation.
- Check haemoglobin and serial lactates.
- Commence hourly urine output measurement.

This list is referred to as 'The Sepsis Six' resuscitation bundle.

Hospital admission\[13\]

For patients identified with 'Red Flag' sepsis, arrange immediate transfer to hospital for further assessment and management. If possible, initiate high-flow oxygen therapy while awaiting transfer.

If no 'Red Flag' signs are identified, the patient may deteriorate rapidly so hospital admission should be carefully considered. Patients aged over 80, patients on chemotherapy or immunotherapy and those unwell despite antibiotic treatment are all particularly high-risk groups. If hospital admission is not considered necessary then careful safety netting (including the need to go to hospital immediately if there are any concerns or deterioration) and review within 24 hours are essential.

Supportive care

- Resuscitation - patients may require intubation and ventilation.
- Intravenous rehydration - aggressively if the patient is shocked.
- Monitoring the patient - this may require measures of central venous pressure (CVP) and urinary output with a catheter.

Specific therapy

The International Guidelines for Management of Severe Sepsis and Septic Shock (2012) provided recommendations for management. The recommendations include\[17\]:

- Intravenous antimicrobials - the choice should include broad-spectrum antibiotics given intravenously. Antivirals and antifungals may also be required, depending on clinical circumstances (eg, in immunocompromised patients). Empirical combination therapy should not be administered for more than 3-5 days. De-escalation to the most appropriate single therapy should be performed as soon as the susceptibility profile is known.
- Initial fluid resuscitation with crystalloids and consideration of the addition of albumin in patients who continue to require substantial amounts of crystalloids (more rapid administration and greater amounts of fluid may be needed in some patients). Fluid challenge technique continued as long as haemodynamic improvement.
- Noradrenaline (norepinephrine) as the first-choice vasopressor to maintain mean arterial pressure ≥ 65 mm Hg; adrenaline (epinephrine) when an additional agent is needed to maintain adequate blood pressure.
- Vasopressin can be added to noradrenaline (norepinephrine), either to raise mean arterial pressure to target or to decrease noradrenaline (norepinephrine) dose.
- Dobutamine infusion administered or added to vasopressor in the presence of myocardial dysfunction or ongoing signs of hypoperfusion despite achieving adequate intravascular volume and adequate mean arterial pressure.
- Avoid use of intravenous hydrocortisone in adult septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore haemodynamic stability.
- Positive end-expiratory pressure (PEEP) for acute respiratory distress syndrome (ARDS).
- Blood glucose management with insulin dosing
- Other management issues include prophylaxis for deep vein thrombosis, use of stress ulcer prophylaxis to prevent upper gastrointestinal bleeding in patients with bleeding risk factors, oral or enteral (if necessary) feeding (rather than either complete fasting or provision of only intravenous glucose within the first 48 hours after a diagnosis of severe sepsis or septic shock).
- Surgery may also be required - eg, wound debridement, abscess drainage.

A protocol for the quantitative resuscitation of severe sepsis and septic shock known as early goal-directed therapy (EGDT) was published in 2001. However, studies have failed to demonstrate any outcome benefit from EGDT\[20\].

The focus of EGDT has shifted to events in the first six hours of care. Early diagnosis, risk stratification using lactate levels, haemodynamic response after a fluid challenge, antibiotics, source control and haemodynamic optimisation are the mainstays of effective management\[21\].

The outcomes of the sepsis programmes are very good and, on average, a 10-20% reduction in overall mortality has been reported\[22, 23\]. In addition to this, length of hospital stay is reduced, resulting in this method being cost-effective\[24\]. Studies have consistently shown that early effective management modulates inflammation, decreases organ failure progression and conserves healthcare resource consumption\[21\].

Prognosis
Severe sepsis causes between 36,000 and 64,000 deaths annually in the UK, with a mortality rate of 35%\textsuperscript{[25]}. Mortality increases to over 40% in the presence of septic shock. There is also evidence that sepsis can have a longer-term effect, worsening the outcome of patients who have chronic diseases\textsuperscript{[9]}.

Early effective treatment is crucial. One study found that each hour of delay in antibiotic administration over the ensuing six hours was associated with an average decrease in survival of 7.6% for patients with septic shock\textsuperscript{[26]}.

Early (within six hours) effective management (achieving goal mean arterial pressure ≥65 mm Hg, CVP ≥8 mm Hg and central venous oxygen saturation ≥70%) improves survival. It has also been shown that achieving these criteria within 18 hours also achieves a significant reduction in mortality\textsuperscript{[27]}.

Elevated lactate levels are associated with in-hospital mortality\textsuperscript{[28]}. The lactate level in sepsis is highly predictive of death, with a lactate level below 2 being associated with 15% mortality and lactate level above 4 associated with 38% mortality\textsuperscript{[29]}.

The prognosis is worse in the elderly. A large American study of long-term mortality (90 days or more after admission) reported an overall mortality of 55% and 1- and 2-year mortality rates were 31% and 43%, respectively. Factors significantly associated with long-term mortality included congestive heart failure, peripheral arterial disease, dementia, diabetes with complications and use of mechanical ventilation. Smoking cessation and cardiac medications were associated with decreased long-term mortality rates\textsuperscript{[30]}.

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**Clinical Editor's comments (September 2017)**

Dr Hayley Willacy recommends the recently released NICE Quality Standard for Sepsis\textsuperscript{[31]}. This focuses on recognition, diagnosis, and early management of sepsis with the aim of improving outcomes for mortality rates, length of stay in hospital and ICU, long-term disability, and organ failure for individuals with sepsis. The five key recommendations are:

1. Individuals with a suspicion of sepsis should be evaluated through a structured set of observations, and risk stratification for severe illness or death should be performed.
2. Individuals with suspected sepsis in acute hospital settings and fulfilling at least one of the criteria for high risk for severe illness or death, should receive the first dose of intravenous (IV) antibiotics and review by a senior clinician within one hour of risk stratification.
3. Individuals with suspected sepsis in acute hospital settings requiring treatment for cardiovascular stability should receive an IV fluid bolus within one hour of risk stratification.
4. Individuals with suspected sepsis in acute hospital settings receiving IV antibiotics or fluid bolus should be seen by a consultant in case of no response within one hour of initial treatment.
5. Individuals with suspected sepsis characterised as low risk for severe illness or death should be educated regarding symptoms to monitor and accessing medical care.

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**Post-sepsis syndrome**

As with any critical illness and prolonged intensive treatment in hospital, people recovering from sepsis may experience physical and psychological difficulties and these difficulties may last for several years.

Physical problems may include lethargy, muscle weakness, breathlessness, chest pains, oedema, arthralgia, poor appetite, visual disturbance, sensory disturbance and recurrent infections.

Psychological difficulties may include anxiety, depression, post-traumatic stress disorder, nightmares, insomnia, poor concentration and memory disturbance.

Produced in collaboration with Dr Ron Daniels of The UK Sepsis Trust.
Further reading & references

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