Sepsis

The body’s response to infection is incredibly complex, involving interactions between a host of substances (interleukins, arachidonic acid metabolites such as prostaglandins, complement, catecholamine, histamines etc) and pathways (coagulatory, fibrinolytic, hormonal etc). Fortunately it is not necessary to understand what is going on at such a level to provide gold-standard treatment. What is necessary is to recognise when infection is progressing to severe sepsis and to act quickly when it has.

- **Sepsis** is defined as the presence of two or more markers for the systemic inflammatory response syndrome (temperature >38°C or <36°C, HR >90/min, RR >20/min, WCC >12 × 10^9/l or <4) plus confirmed or suspected infection.
- **Severe sepsis** is the addition of organ dysfunction or hypoperfusion, or hypotension. Signs of organ dysfunction and hypoperfusion include:
  - oliguria
  - confusion
  - metabolic (lactic) acidosis
  - poor peripheral perfusion
- **Septic shock** is the persistence of severe sepsis and hypotension despite adequate fluid resuscitation.

It is worth noting that the definition of “sepsis” is fairly all-encompassing – a lot of people with simple flu would be included within its terms. Bear in mind too that these are somewhat artificial definitions – patients present somewhere along a continuum rather than in discrete categories.

Why infection sometimes progresses to severe sepsis and septic shock is unclear, but it seems to be a massive over-reaction by the body in which the normally finely balanced homeostatic mechanisms are deranged. The inflammatory, fibrinolytic and coagulatory cascades get carried away. Microvascular blood flow is severely compromised resulting in end-organ dysfunction. This is well-demonstrated by De Backer et al, 2002 (and its separate online data supplement, which shows videos of sublingual blood in a normal volunteer and a patient with sepsis).

The key aim of initial treatment is to try to reverse the hypoperfusion and ensure adequate delivery of oxygen to end-organs.

**Oxygen delivery** is determined by:

1. **The amount of oxygen carried in the blood**
   This depends primarily on haemoglobin concentration and oxygen saturation.

2. **The amount of blood reaching the tissues**
   This depends on cardiac output (stroke volume x heart rate) and peripheral perfusion.

So, optimising oxygen delivery means careful optimisation of the circulating volume with fluid (and sometimes blood), provision of oxygen and high quality supportive treatment with inotropes and vasoconstrictors. At the same time, the focus should be
to identify and treat the source of infection, remembering that “surgical” sepsis needs surgical treatment as well as antibiotics.

Mortality for septic shock is as high as 50% and the morbidity can be huge. In the last five years a considerable body of work has emerged to support the notion that early recognition and treatment can be vital. Rivers et al (2001) found that early goal-directed invasive therapy in the emergency department can reduce mortality by 16% (absolute reduction). Their protocol goes beyond that which can be applied in the average UK emergency department currently, but has been incorporated into the Surviving Sepsis Campaign guidelines (Dellinger et al, 2004 [pdf]) that represent the views of a broad range of international bodies.

**Initial management** follows a simple ABC approach:

- Ensure patent airway, initially with simple measures, but recognise that intubation may be needed to maintain patency, and to protect against aspiration in an obtunded patient.
- Provide lots of oxygen: now is not the time for careful titration of oxygen for fear of precipitating CO₂ retention!
- Circulation – get good access and use it: rapid bolus of crystalloid or colloid.
- Exclude or treat hypoglycaemia (particularly common in septic infants).
- Bloods: full blood count, clotting profile (likely to be deranged), blood cultures, urea & electrolytes as a minimum.
- Blood gas: establish degree of metabolic acidosis.
- Intravenous antibiotics, depending on clinical assessment of likely source of infection as soon as possible.
- Look for the source of infection: thorough examination; chest X-ray; culture everything.
- Monitor response to fluids: perfusion, vital signs, improvement in end-organ function, repeated ABGs.
- Be prepared to institute invasive monitoring if no rapid improvement occurs despite full care.
- Get critical care involved **early**.

**Central venous oxygen saturations (ScvO₂)**

In addition to the supportive measures above, the Surviving Sepsis Campaign guidelines identify lactic acidosis as a marker of severe sepsis that may be present even when the blood pressure is normal. They provide a clear rationale for the role of inotropes and vasoconstrictors, guided by invasive monitoring, in the early treatment of sepsis and use ScvO₂ as a marker of inadequate tissue oxygen delivery. Central venous oxygen saturation is lower than oxygen saturation (SaO₂) because tissues extract oxygen from the circulation. The less oxygen delivered to the tissues, the higher the percentage of oxygen extracted and the lower the ScvO₂. So a low ScvO₂ is suggestive of inadequate delivery of oxygen to the tissues by the circulation. Bear in mind that simply increasing the amount of oxygen the patient is breathing will not increase the oxygen delivery if the SaO₂ is already normal. Instead it is necessary to optimise cardiac output, peripheral vascular resistance and haemoglobin concentration.
Pulmonary oedema

As well as poor microvascular blood flow, sepsis leads to leaky capillaries. This can be a particular problem in the lungs. Providing enough intravenous fluid to optimise cardiac output can lead to pulmonary oedema, particularly if there is a degree of myocardial depression (probably as a result of various circulating cytokines). In this situation the only real option is ventilatory support – possibly non-invasively, but often by intubation.

Pharmacological intervention

Current evidence supports the use of steroid supplementation in septic patients who fail to show an adequate cortisol spike in response to Synacthen, and the use of intravenous insulin by sliding scale to control blood glucose in diabetics and non-diabetics.

The over-stimulation of the cytokine, coagulant and fibrinolytic systems has led to numerous attempts at pharmacological intervention over the years from high-dose steroids to anti-tumour necrosis factor antibodies. None has shown consistent benefit, but a recent innovation, activated protein C, has shown some promise and has been approved for use by the National Institute for Health and Clinical Excellence (NICE) in specific circumstances although a recent Cochrane review has been less positive (Martí-Carvajal et al., 2007). Interest has also arisen in the role of statins in modifying the inflammatory response with potential benefit shown in retrospective studies (Gao et al., 2008).

Pitfalls

- Severe sepsis and septic shock are difficult conditions to treat. The aim should be to recognise the signs of sepsis and intervening before it is too late.
- Ensure adequate fluid resuscitation.
- Ensure appropriate antibiotics are given as soon as possible after a diagnosis is made and cultures are taken. Make sure they are given before the patient leaves the emergency department.
- Pay close attention to vital signs – all the evidence shows that many patients who end up on ICU were showing clear signs of deterioration that went unrecognised in the ward or in the emergency department. If the respiratory rate or heart rate is abnormal consider why.
- Look at ABG results closely and pay particular attention to CO₂, bicarbonate and base excess. Do not miss an early compensated metabolic acidosis.
- Sick patients need a high level of care – involve the critical care team early.
- Patients with sepsis have leaky capillaries. An appropriate level of fluid resuscitation can still lead to pulmonary oedema – early intubation may be needed.
- Patients with sepsis can decompensate and deteriorate rapidly – do not delay referral to critical care.