

# Trends and controversies in the management of sepsis

## Introduction

Patients with sepsis are frequently encountered in emergency departments and hospital wards, but may be at different stages of the disease process. In the UK, Intensive Care National Audit and Research Centre data collected in 2005 estimated that 36 800 patients per year die of sepsis, more than the annual mortality from breast cancer and bowel cancer combined (Daniels, 2007). International guidelines were published in 2004 and updated in 2008 (Dellinger et al, 2008) aiming to improve outcomes from sepsis syndromes through promotion of evidence-based practice. While components of the guidelines continue to be the subject of debate, prompt appropriate action will have the greatest impact on mortality and morbidity. This article gives a practical, evidence-based approach to the early management of the septic patient and outlines some areas of controversy.

## Definitions, recognition and severity stratification

Traditionally, sepsis has been defined as the presence of systemic manifestations of inflammation with a proven or presumed focus of infection. Severe sepsis and septic shock are further severity grades, based on the presence of organ dysfunction, organ hypoperfusion or hypotension, associated with worse outcomes (Levy et al, 2003).

In an effort to improve recognition of sepsis, particularly severe sepsis, the Surviving Sepsis campaign included inflammatory markers (C-reactive protein and procalcitonin) and more prescriptive indicators of organ dysfunction (Table 1) in the criteria for diagnosing sepsis (Dellinger et al, 2008). The severe sepsis category was also modified to encompass evidence of

hypoperfusion, hypotension at any time or organ dysfunction (Figure 1). On a practical ward level, sick patients can be categorized into those with sepsis or severe sepsis, the latter predicting significant morbidity and mortality and demanding early aggressive treatment. Table 2 outlines other factors which predict adverse outcome.

## Goal-directed therapy

Heart rate and arterial blood pressure do not accurately reflect the adequacy of resuscitation (Wo et al, 1993; Shoemaker et al, 2000). Inadequate tissue perfusion may continue despite restoration of blood pressure, while tachycardia secondary to the initial neurohormonal stimuli can persist despite adequate resuscitation (Wo et al, 1993; Shoemaker et al, 2000). Targeting heart rate reduction may therefore lead to under- or over-resuscitation. Goal-directed therapy uses standard methods of resuscitation, e.g. fluid administration, vasopressors and inotropes, to meet predetermined targets that reflect global tissue perfusion.

In 2001, Rivers et al showed that achieving central venous oxygen saturations (ScvO<sub>2</sub>) >70% in the first 6 hours of treatment for emergency department patients with severe sepsis and septic shock improved outcome, with significant reductions in 28-day mortality, improvements in APACHE II scores, simplified acute physiology II values, multiple organ dysfunction scores and coagulation indices. From a physiological perspective, ScvO<sub>2</sub> (measured in the superior vena cava from a central line) or mixed venous oxygen saturation (pulmonary artery, from a Swan-Ganz catheter) reflects the balance between oxygen supply and consumption and is often regarded as a surrogate marker of the adequacy of oxygen delivery. 'Early goal-directed therapy' targets (Table 3) implemented by Rivers et al form the basis of sepsis resuscitation in international guidelines.

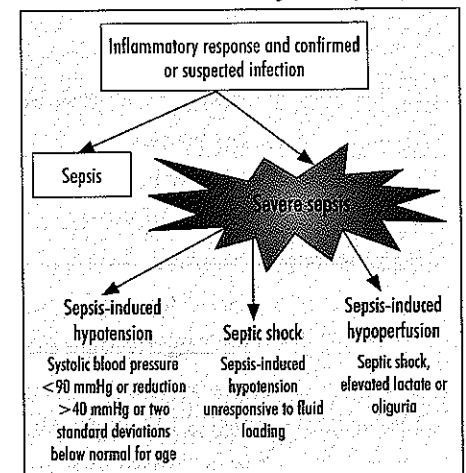
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**Table 1. Thresholds for identification of severe sepsis on the basis of organ dysfunction**

Organ system	Threshold
Respiratory	Lung injury pattern with PaO <sub>2</sub> :FiO <sub>2</sub> <250 in absence of pneumonia or <200 in presence of pneumonia
Renal	Urine output <0.5 ml/kg/hr for 2 hours despite adequate fluid resuscitation Creatinine > 176.8 μmol/litre
Hepatic	Bilirubin > 34.2 μmol/litre
Blood	Platelet count <100 x10 <sup>9</sup> /litre
Coagulation	International normalized ratio >1.5

FiO<sub>2</sub> = inspired oxygen fraction percentage; PaO<sub>2</sub> = oxygen partial pressure (mmHg). From Dellinger et al (2008)

**Figure 1. Modified severity classification of sepsis based on the 2008 Surviving Sepsis campaign recommendations. From Dellinger et al (2008).**



**Table 2. Characteristics which determine the baseline risk of adverse outcome including mortality and potential to respond to therapy in patients with sepsis**

Predisposition – premorbid illness with reduced probability of short-term survival, cultural or religious beliefs, age, sex
Insult infection – culture and sensitivity of infecting pathogens, detection of disease amenable to source control
Response to infection – e.g. SIRS, other signs of sepsis, shock, C-reactive protein
Organ dysfunction – number of failing organs or composite score

SIRS = systemic inflammatory response syndrome. From Levy et al (2003), Dellinger et al (2008), Rubulotta et al (2009)

Miss Kaji Sritharan is Specialist Registrar in Vascular Surgery, St Thomas' Hospital, London SE1 7EH, Dr Chris Jones is Specialist Registrar in Anaesthesia and Intensive Care, St Georges Healthcare NHS Trust, London and Dr Mamoun Abu-Habsa is Specialist Registrar in Intensive Care Medicine, Oxford Radcliffe Hospitals

Correspondence to: Miss K Sritharan

## Fluid resuscitation and circulatory support: a practical approach

Fluid loading is the most appropriate initial step in sepsis resuscitation and should aim to restore a presumed safe perfusion pressure for the critical organs – usually fluid boluses of 250–500 ml to target an minimum mean arterial pressure of 65 mmHg. However, adequate perfusion requires good blood flow as well as an adequate perfusion pressure, so such the 65 mmHg mean arterial pressure target should be regarded as a ‘safety net’, not a marker of adequate resuscitation. If fluid resuscitation alone does not reach this target then vasopressors may be required – this is not uncommon in septic shock. Owing to their short half-life, familiarity with their dosing and understanding of their risks, noradrenaline or adrenaline are the most common vasopressors used.

The Surviving Sepsis campaign advocates vasopressor therapy at a predetermined central venous pressure threshold of 8 mmHg (12 mmHg for ventilated patients), although central venous pressure does not accurately reflect cardiovascular filling status (Michard and Teboul, 2002; Osman et al, 2007). Echocardiography and Doppler-based cardiac output monitoring can help guide fluid resuscitation if there is ongoing evidence of organ hypoperfusion (Charron et al, 2006; Chytra et al, 2007).

Once a safe mean arterial pressure is achieved, venous blood sampling and saturation (ScvO<sub>2</sub>) measurement from the superior vena cava (via a central line) can give an impression of global tissue perfusion or the balance between oxygen supply and consumption to further guide fluid resuscitation requirements. Achieving ScvO<sub>2</sub> saturation >70% within 6 hours was a key target in Rivers’ approach and some patients with a presumed low cardiac output state need inotropic support to achieve this. More contentious is red cell transfusion to improve

the oxygen-carrying capacity in patients with a haematocrit <30%, unable to reach their ScvO<sub>2</sub> target (Rivers et al, 2001). Blood transfusion in sepsis is discussed later.

A major drawback is the inherent assumption that ScvO<sub>2</sub> accurately represents adequate resuscitation in all patients with sepsis: patients may present with an elevated ScvO<sub>2</sub> of 80% or higher despite evidence of organ hypoperfusion. ScvO<sub>2</sub> values around 70% may suggest adequate resuscitation while elevated values may represent poor oxygen extraction secondary to cellular dysfunction (Reinhart and Bloos, 2005); a transition to a phase where oxygen consumption is independent of delivery (Hayes et al, 1994). The latter is most likely to be seen in patients with a delayed presentation, prolonged septic shock or a delay in recognition of shock. In the presence of organ dysfunction, these patients should be managed with organ support at recognized thresholds (e.g. haemofiltration in renal failure with acidosis). Titration of fluids and vasoactive agents is more difficult and the benefits, beyond maintaining organ perfusion, are less clear.

While early goal-directed therapy may appear practical and logical in most settings, in sepsis it is founded on a single-centre open study (Rivers et al, 2001). Multicentre validation studies are in progress in the USA and Australasia, and will shortly begin in the UK.

## Mechanical ventilation

A significant proportion of patients with severe sepsis require mechanical ventilation to address unsatisfactory gas exchange or patient fatigue, or to reduce oxygen consumption in patients with persistent global tissue hypoperfusion. A lung protective strategy should be used as these patients are at significant risk of acute lung injury or acute respiratory distress syndrome. A tidal volume target of 6 ml/kg is recommended and the plateau airway pressure should not be allowed to exceed 30 cmH<sub>2</sub>O (Acute Respiratory Distress Syndrome Network, 2000). Some degree of positive end expiratory pressure is recommended to prevent basal atelectasis but the level depends on the individual’s gas exchange, haemodynamic status and presence of established lung injury (Dellinger et al, 2008). Patients should be nursed with the head of the bed raised to 30–45° to minimize the risk of ventilator-associated pneumonia, particularly patients

receiving enteral nutrition, but this is not easy even in a randomized controlled trial (van Nieuwenhoven et al, 2006).

For patients with established acute lung injury or acute respiratory distress syndrome, a conservative fluid strategy with a tightly controlled cumulative 7-day fluid balance improved oxygenation and decreased the number of days of mechanical ventilation and intensive care unit length of stay without an increase in non-pulmonary organ failure (Wiedemann et al, 2006). Adequate goal-directed fluid resuscitation in the first 42–45 hours coupled with a neutral to negative fluid balance in the subsequent 7 days may significantly reduce mortality in patients with established lung injury (Rivers, 2006; Murphy et al, 2009).

## Steroids: to give or not to give?

Much of the basis for the use of steroids in sepsis is derived from two key multicentre trials. Annane et al (2002) showed that treatment with low doses of hydrocortisone and fludrocortisone significantly reduced mortality and reversed shock without increasing adverse events in patients with vasopressor-resistant shock and relative adrenal insufficiency. The second larger trial, CORTICUS, evaluated use of intravenous hydrocortisone in a much broader group of patients with septic shock. They failed to show any mortality benefit with steroid therapy regardless of the patient’s adrenal responsiveness to corticotrophin, but more rapid resolution of septic shock was seen in the steroid group (Sprung et al, 2008).

Steroid therapy is associated with well-recognized side effects such as myopathy and increased susceptibility to infections. Since no clear mortality benefit has been proven, steroids are only advocated in cases of severe sepsis which is unresponsive to fluid resuscitation and vasopressor therapy (Dellinger et al, 2008). Adrenocorticotropic hormone stimulation tests are not useful or required.

## Antibiotics and source control

In patients with severe sepsis, broad-spectrum antibiotic therapy is recommended until the causative organism is identified, after which antibiotic therapy should be adjusted accordingly (Dellinger et al, 2008). Blood cultures should be taken before starting antibiotics, since sterilization of blood cultures can occur within hours of the first dose, but this should not delay antibiotic

**Table 3. Recommended goals of initial resuscitation in severe sepsis**

Central venous pressure 8–12 mmHg

Mean arterial pressure ≥65 mmHg

Urine output ≥0.5 ml/kg/hour

Central venous (superior vena cava) or mixed venous oxygen saturation ≥70% or ≥65% respectively

From Rivers et al (2001), Dellinger et al (2008)

administration – Kumar et al (2006) found that each hour's delay in antibiotic administration was associated with an average decrease in survival of 7.6%. In an observational study on patients with septic shock, delayed antibiotic administration was the only independent predictor of in-hospital mortality (Garnacho-Montero et al, 2006). Conversely, Harbarth et al (2007) showed that inappropriate antibiotic therapy does not adversely affect outcome in critical illness. While the use of early empirical antibiotic therapy appears safe and reasonable, this is largely based on a single study.

## Glycaemic control in sepsis

Patients with sepsis are at increased risk of hyperglycaemia, related to the severity of sepsis (Waesche et al, 2008). Randomized control trials have found a reduction in mortality with insulin therapy. Other beneficial effects include earlier weaning from mechanical ventilation, and reductions in organ dysfunction, polyneuropathy, rate of blood transfusion and length of intensive care unit stay (Finney et al, 2003; Pittas et al, 2006).

Insulin therapy is not without complications and is associated with a high incidence of hypoglycaemia. This may in part be explained by variability in the target glucose levels and insulin infusion protocols used (Finney et al, 2003; Wilson et al, 2007; Dellinger et al, 2008). The Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study, which recruited 6104 critically ill medical and surgical patients, evaluated the effect of intensive glucose control (target blood glucose 4.5–6.0 mmol/litre) compared to conventional glucose control (target <10.0 mmol/litre) (Finfer et al, 2009). NICE-SUGAR reported frequent severe hypoglycaemia in the intensive-control group compared to the conventional glucose control group (6.8% *vs* 0.5%), with no significant difference in length of stay in intensive care unit or hospital, or mechanical ventilation requirement between the two groups. Increased mortality rates were seen in the intensive glucose control group (Finfer et al, 2009).

Dellinger et al (2008) advocate the use of intravenous insulin to reduce blood glucose levels in patients with severe sepsis and hyperglycaemia admitted to the intensive care unit using a validated protocol with a

target glucose of 8.3 mmol/litre. In view of the NICE-SUGAR findings, this should perhaps be revised to a target glucose of 6.0–10.0 mmol/litre; either way, some degree of glycaemic control is necessary.

## Recombinant activated protein C

The rationale for the use of activated protein C is derived from two large randomized control trials. PROWESS evaluated the use of human recombinant activated protein C in 1690 patients and showed significant reductions in mortality in patients with severe sepsis (Bernard et al, 2001). Subgroup analysis showed this reduction in mortality to be greater in those at higher risk of death as defined by higher APACHE II scores and failure of two or more organs.

The ADDRESS trial recruited 2613 patients at low risk of death, most of whom had APACHE II scores <20 or single organ dysfunction, and failed to demonstrate any significant mortality benefit with the use of activated protein C (Abraham et al, 2005). Activated protein C use is associated with an increased risk of serious intracranial as well as gastrointestinal bleeding (Bernard et al, 2001; Abraham et al, 2005), and registry data suggest that the actual incidence is higher than reported (Dellinger et al, 2008). The lack of clear mortality benefit in low risk patients, coupled with the risk of bleeding, fails to justify the use of activated protein C in this group. Human recombinant activated protein C is only advocated in patients with sepsis-induced organ dysfunction with a high risk of death, in the absence of any contraindications, in which case early administration may be associated with better outcomes (Vincent et al, 2005).

## Blood transfusion

The optimum haemoglobin level for a patient with sepsis has not been established. Hebert et al (1999) found no increase in mortality with haemoglobin levels of 7–9 g/dl compared to levels of 10–12 g/dl in the non-shocked patient. However, this study enrolled only 12% of all potential patients and used non-leukodepleted blood, so it is unclear whether its conclusions are valid for the use of leukodepleted blood (current practice in the UK). Some patients, such as those with ischaemic heart disease, benefit from higher haemoglobin levels, so threshold levels for transfusion should be evaluated for each individual patient (Nichol, 2008).

From an organ perfusion perspective, Dellinger et al (2008) recommend a target haematocrit of 30% as part of initial goal-directed therapy in patients with inadequate oxygen delivery. Transfusion risk-benefit has not been adequately studied in this phase, so this is contentious.

Unless there is active bleeding or a planned invasive procedure, fresh frozen plasma is not advised to correct clotting abnormalities. Platelet transfusion is advised when counts are <5×10<sup>9</sup>/litre, and if counts are 5–30×10<sup>9</sup>/litre and there is a significant risk of bleeding. Platelet counts of ≥50×10<sup>9</sup>/litre are required if surgery or an invasive procedure is planned (Dellinger et al, 2008).

## Deep vein thrombosis prophylaxis

Studies of deep vein thrombosis in sepsis are lacking. Deep vein thrombosis prophylaxis in patients with sepsis is supported by evidence from non-surgical hospital admissions and intensive care unit patients with a high proportion of sepsis, where the incidence of deep vein thrombosis is 13–31% (Geerts et al, 2002) and low molecular weight heparin and unfractionated heparin have equivalent efficacy and safety profiles. A single arm multicentre trial found that even in critically ill patients with severe renal insufficiency, low molecular weight heparin is not associated with excessive anticoagulation because of accumulation (Douketis et al, 2008). The choice of drug is largely influenced by cost, but unfractionated heparin, although cheaper, requires twice daily rather than once daily administration.

If heparin is contraindicated mechanical prophylactic devices should be used, e.g. graduated compression stockings.

## Stress ulcer prophylaxis

The presumed benefit of stress ulcer prophylaxis in patients with sepsis comes from studies on general intensive care unit patients. Of these patients, 20–25% had sepsis and stress ulcer prophylaxis using a H<sub>2</sub>-receptor blocker or proton pump inhibitor appeared to reduce clinically significant upper gastrointestinal bleeding. There was no evidence of a benefit of stress ulcer prophylaxis outside the intensive care unit. However, a more recent meta-analysis did not provide adequate evidence for the use of ranitidine and sulcralfate to prevent gastrointestinal bleeding in the critical care setting. Ranitidine use is associated with an increased risk of pneu-

monia (Messori et al, 2000). A retrospective study of general inpatients found a significant association of proton pump inhibitor but not H2 blockers use with pneumonia (Herzig et al, 2009). Prophylactic acid suppression is an independent risk factor for development of *Clostridium difficile* diarrhoea (Leonard et al, 2007).

## Conclusions

The high morbidity and mortality from sepsis continues to generate clinical and academic interest. The Surviving Sepsis campaign guidelines are an attempt to develop a universal evidence-based population approach to the management of the critically ill septic patient. However, they are not without controversy and much of the criticism relates to the lack of expert consensus and the use of weak methodologies in the interpretation of evidence.

For many patients, early identification and early correction of circulatory deficits form the mainstay of treatment and a targeted or goal-directed therapy approach is useful to ensure that deficits are adequately reversed and treatment does not harm patients. Care of the patient with severe sepsis requires a multidisciplinary approach and glycaemic control, antibiotic practice, blood transfusion and prophylactic interventions should be considered in terms of the evidence available and the individual patient. *BJHM*

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## KEY POINTS

- Patients have severe sepsis if they present with hypotension, evidence of hypoperfusion or organ dysfunction.
- Early identification and correction of circulatory deficits associated with severe sepsis may reduce morbidity and mortality.
- The main components of therapy continue to be targeted fluid resuscitation and circulatory support to maintain a perfusion pressure for critical organs.
- Highly elevated central venous oxygen saturations suggest poor oxygen extraction and cellular dysfunction; these patients are more difficult to manage beyond offering appropriate organ support.