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Sepsis: an update for physicians

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Sepsis is defined as the systemic inflammatory response syndrome due to confirmed or suspected infection.[1] Currently, there are more than 31,000 admissions to intensive care units (ICUs) in England, Wales and Northern Ireland each year due to sepsis, resulting in more than 14,000 deaths. These numbers are increasing.[2] Outcome is related to illness severity as patients progress through severe sepsis (acute organ dysfunction secondary to sepsis) and septic shock (severe sepsis with hypotension refractory to fluids) with mortality rates up to 50%.[3] In order to improve outcomes, evidence-based guidelines have been published as part of the international Surviving Sepsis Campaign (SSC).[4] This article is partly based on these recommendations but also provides additional, more recent data.

Early recognition of pathology and timely implementation of therapy improve outcomes in sepsis.[5,6] Even short delays in administering antibiotics are associated with increased mortality.[6] Wherever possible, patients must receive these within one hour of presentation. Blood cultures should ideally be drawn immediately prior to antimicrobial administration to maximise the potential for positive microbiology as they will often be rendered sterile by systemic antimicrobial therapy. The samples should be taken peripherally and from indwelling vascular access devices (unless <48 hours since insertion) to help ascertain whether:

- a peripherally grown organism is the primary pathogen (more likely if grown from more than one site), or
- the indwelling catheter is the source of infection.[4]

Appropriate samples should be taken from other potentially infected areas, as guided by the clinical history and examination.

In severe sepsis, initial antibiotic treatment should be broad spectrum as the consequences of failing to treat the pathogenic organism are potentially catastrophic.[6] Attention must be paid to the tissue penetration of the chosen antimicrobials, depending on the site of infection, and also to local pathogenic resistance patterns. Any recently used therapies are probably best avoided if there is concern about a new infection with a potentially resistant organism. Antibiotic therapy should be reassessed regularly with the spectrum narrowed when possible, ideally on the basis of positive microbiological data, to prevent superinfection and development of resistance.

Investigation of source of sepsis

Appropriate source control should be performed promptly (at least within six hours of presentation). It may involve debridement of necrotic tissue, evacuation of pus or removal of an infected catheter. Material should be sent for culture wherever possible to help guide antimicrobial treatment. Imaging may be required to locate the infected site, but care must be taken to ensure unstable patients are not exposed to unnecessary transfer and intervention. These investigations should take the form of the least destabilising procedure.[4]

Resuscitation

Resuscitation in septic shock should follow a protocol titrated against physiological goals during the initial six hours. Such 'goal directed' therapy reduced hospital mortality by 16% in a single-centre trial when commenced early in severe sepsis and septic shock.[5] This study incorporated several measures to optimise oxygen delivery by increasing cardiac output and maximising oxygen content, so it is difficult to specify which intervention produced the mortality benefit.

A further trial performed across two sites in the UK used a series of similar goals packaged together as a 'bundle', to be instigated within six hours of presentation with sepsis. Non-compliance was associated with a more than twofold increase in hospital mortality.[7] A UK multicentre trial is currently assessing the clinical efficacy and cost-effectiveness of resuscitation carried out with such protocols.[8]

Resuscitation goals

The goals of resuscitation, as recommended by the SSC, include:

- central venous pressure 8–12 mmHg or 12–15 mmHg if mechanically ventilated, there is diastolic dysfunction, intra-abdominal hypertension or significant pulmonary artery hypertension
- mean arterial pressure (MAP) 65 mmHg or above
- urine output 0.5 ml/kg/h or higher
- central venous (superior vena cava) oxygen saturation ($ScvO_2$) at least 70% or mixed venous oxygen saturation (SVO_2) 65%.[4]

$ScvO_2$ and SVO_2 targets are used as a measure of adequate oxygen delivery. Normalising serum lactate can be used as an alternative target.[9]

Resuscitation fluids

Resuscitation may be performed with boluses of either colloid (500 ml) or crystalloid (1,000 ml), reflecting an absence of definitive evidence suggesting the superiority of either type of fluid in this context. Initially, they should be infused rapidly (over ca 30 min), with boluses repeated whilst haemodynamics continue to improve.

Red cell transfusion may be required and should target a haemoglobin concentration of 10 g/dl or more in the initial stages of resuscitation.[4] In many cases of severe sepsis and, by definition, in septic shock, fluid resuscitation will not be sufficient to achieve these goals, indicating the requirement for cardiovascular support.

Vasopressors

Vasopressors increase systemic vascular resistance and therefore blood pressure. Both noradrenaline and dopamine are recommended in the 2008 SSC guidelines.[4] However, a recent large trial has demonstrated that dopamine infusion resulted in a significantly greater incidence of adverse events, particularly arrhythmias.[10] Noradrenaline should now be considered the preferred vasopressor, with the infusion rate titrated against the target MAP (this may need individual revision depending on age and comorbidities).

Septic shock is associated with a relative deficiency of vasopressin. In recent years there has been an increased level of interest in its use as an adjunct vasopressor. In this context, vasopressin binds to vascular smooth muscle, producing vasoconstriction with minimal osmotic effects. In the Vasopressin And Septic Shock Trial (VASST), a multicentre randomised controlled trial (RCT) comparing vasopressin to noradrenaline in adults with established septicshock, there was no significant mortality benefit in the whole study population. However, the a priori defined subgroup analysis showed a survival benefit in patients with less severe shock.[11]

Post hoc analysis of the VASST data supports the theory that vasopressin may have protective effects on renal function. When the risk, injury, failure, loss, end-stage (RIFLE) criteria[12] (Table 1) were applied to patients to categorise renal dysfunction at study entry, those patients receiving vasopressin in the risk category had significantly lower rates of progression to either renal failure or loss, as well as a reduced requirement for haemofiltration.[13] The VASST study also found that a combination of vasopressin and steroids was associated with significantly lower rates of mortality and organ dysfunction compared with noradrenaline and steroids.[14] This may reflect a degree of interaction between the drugs because patients treated with steroids and vasopressin had higher circulating vasopressin levels than those receiving vasopressin without steroids. The treatment implications of these findings are currently unclear, but another planned UK trial aims to answer some of these uncertainties.[15]

Other abnormalities associated with sepsis

Effects on the myocardium

Sepsis can suppress the myocardium, with left ventricular dysfunction seen in up to 50% of patients with persistent septic shock.[16] In the context of an adequate circulating intravascular volume but reduced cardiac output, inotropic support is indicated to augment oxygen delivery. Adrenaline can be used, but is associated with tachyarrhythmias, raised lactate and reduced splanchnic perfusion. Current evidence supports dobutamine use.[5]

Adrenal insufficiency

Many septic patients have occult adrenal insufficiency and display vascular insensitivity to circulating catecholamines. In a multicentre RCT enrolling septic shock patients responding poorly to vasopressors, steroid supplementation reduced both shock duration and mortality.[17] A subsequent multicentre RCT enrolling patients all of whom had septic shock, found hydrocortisone treatment led to earlier shock resolution. However, there was no mortality benefit and an increased rate of adverse events.[18] Current guidelines now recommend low-dose hydrocortisone (⩽300 mg/day) only for patients who have septic shock poorly responsive to fluid and vasopressors (ie refractory shock).[4]

Coagulation abnormalities

Sepsis produces abnormalities of coagulation ranging from microvascular thrombosis to disseminated intravascular coagulation, as well as derangement of many coagulation markers including reduced circulating levels of protein C.[19] Deficiencies of this serine protease are thought to contribute to abnormal coagulation processes; recombinant human

Table 1. Use of risk, injury, failure, loss, end-stage (RIFLE) criteria to describe acute renal dysfunction.

	Criteria	
RIFLE	**GFR**	**Urine output**
Risk	Increased serum creatinine × 1.5 or decreased GFR >25%	<0.5 ml/kg/h × 6 h
Injury	Increased serum creatinine × 2 or decreased GFR >50%	<0.5 ml/kg/h × 12 h
Failure	Increased serum creatinine × 3 or decreased GFR >75% or increased serum creatinine ⩾44 μmol/l if baseline ⩾350 μmol/l	<0.3 ml/kg/h × 24 h or anuria × 12 h
Loss	Persistent acute renal failure = complete loss of renal function for >4 weeks	
End-stage	End-stage kidney disease (>3 months)	

GFR = glomerular filtration rate.
The change in serum creatinine and GFR are based on the patient's normal baseline values.

activated protein C (rhAPC) is used as an adjunct treatment in sepsis.

A multicentre RCT randomising patients with severe sepsis to receive either rhAPC or placebo was stopped early due to efficacy as treatment produced a 6.1% reduction in 28-day mortality.[20] Subgroup analysis and additional studies revealed this to be confined to those patients who had severe sepsis and a high risk of death (in Europe generally defined as more than one acute organ system dysfunction). The use of rhAPC in sepsis increases the risk of bleeding; therefore, the balance between bleeding risk and expected clinical benefit must be carefully considered. An ongoing trial will hopefully clarify the risk/benefit ratio.[21]

Other procedures aimed at improving outcome

Many other measures are performed in the ICU to improve outcome in sepsis including:

- protective ventilatory strategies (minimising pressure and volume trauma)
- elevating the head of the bed to minimise aspiration
- gastric protection to prevent stress ulceration
- controlling blood glucose levels
- sedation protocols
- ensuring prophylaxis against venous thromboembolism.

Although mortality rates from severe sepsis and septic shock remain high, data are emerging to suggest that outcomes can be improved by following evidence-based guidelines.[22]

Conflict of interests

ACG is an inventor on a patent application submitted by the University of British Columbia related to the use of vasopressin in septic shock. He has received research funds and consulting fees from Sirius Genomics, and speaker and advisory board fees from Eli Lilly & Co. ACG is in receipt of an NIHR clinician scientist fellowship award, and is grateful for funding through the NIHR-BRC funding scheme. Both authors have also received research support from the Intensive Care Foundation.

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Key points

- Mortality from severe sepsis and septic shock remains high
- Prompt antimicrobials/source control reduce mortality
- Initial resuscitation should be titrated against physiological goals
- Vasopressors are frequently required; noradrenaline should be considered the preferred agent
- Steroid use should be reserved for refractory shock

KEY WORDS: resuscitation, sepsis, septic shock, treatment guidelines, vasopressors

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