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CLINICAL REVIEW

Management of sepsis

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This is the second of two reviews—the first discussed the definition, epidemiology, and diagnosis of sepsis, whereas this one focuses on management and outcome. Management of sepsis can conveniently be divided into general supportive measures and specific treatment.

What are the general supportive measures?

Circulatory compromise arises from the combination of vasodilatation, capillary leak, and reduced myocardial contractility, and needs early correction. Whether crystalloids or colloids are better for volume resuscitation remains unresolved. Few people now use human albumin after a controversial meta-analysis concluded that albumin was associated with a 6% excess mortality.[1] A subsequent randomised controlled trial found no difference in any of the outcome measures examined, including mortality.[2]

Another question is how to gauge the adequacy of fluid resuscitation. The pulmonary artery catheter has not been shown to be associated with either harm or benefit,[3 4] and its use is declining. Clinical end points (box 1) remain useful, although some centres are also using oesophageal Doppler or pulse contour analysis. These methods provide information on the effect of fluid loading on cardiac output and stroke volume. In ventilated patients, variation in stroke volume can be used as an index of preload.

Catecholamines are needed when fluids are insufficient to restore adequate tissue perfusion. The quality of evidence on which to base the choice of agents is poor. Currently, either noradrenaline (norepinephrine) or dopamine is recommended as first line agent. Noradrenaline increases the blood pressure more rapidly and reliably than dopamine and improves renal function, but it produces only a modest rise in cardiac output. Its effects on the liver and gastrointestinal mucosa are unpredictable. Dopamine, on the other hand, despite increasing splanchnic blood flow at low doses, does not increase oxygen consumption in the gut or improve hepatic function. Moreover, unease is growing about its negative effects. These include reduction of gut motility, hypoprolactinaemia mediated immunosuppression, reduced anabolism, and impaired thyroid function. In a recent observational study, dopamine was associated with an increased risk of death in hospital.[5] At high doses, dopamine may precipitate supraventricular arrhythmias. Adrenaline (epinephrine) is now rarely used as a single agent, if at all. It causes a fall in splanchnic perfusion and, in some cases, a lactic acidosis. In the future, an increased understanding of the effects of adrenoreceptor up regulation and down regulation, adrenoreceptor gene polymorphism, and free radical alterations to adrenoreceptor activation may lead to better use of catecholamines.

The role of non-catecholamine drugs, such as vasopressin, levosimendan, methylene blue, and the phosphodiesterase inhibitors, to support the circulation in sepsis remains to be clarified. Timeliness of the intervention and attention to subtle signs of persisting tissue hypoperfusion are important. Survival is increased when volume loading to standard end points (box 2) is supplemented, where necessary, by blood, catecholamines, and even mechanical ventilation.[6]

Many patients with severe sepsis, even without pulmonary sepsis, need respiratory support because of the combined effects of increased ventilatory demand, hypoxaemia, and respiratory muscle dysfunction.[7] Some patients develop the acute respiratory distress syndrome. The duration of mechanical ventilation can be reduced by daily interruptions of sedation,[8] and a 9% increase in survival has been achieved in patients with acute lung injury or acute respiratory distress syndrome by using low tidal volumes (6 ml/kg ideal body weight).[9]

Renal failure occurs in 20-50% of patients, depending on severity. Some evidence shows that high volume haemofiltration temporarily reduces the need for vasopressors,[10] but whether this translates into any long term advantages, in terms of either renal function or survival, has not been proved.

Nutrition is another area in which high quality data are scarce, particularly among non-surgical patients. In general, early enteral nutrition is recommended,[11] but this was associated with increased morbidity in the only study in non-surgical patients.[12] Furthermore, supplements designed to boost the immune system,

Box 1 | Clinical and functional end points for titration of fluid resuscitation

- Sustained increase in blood pressure
- Sustained increase in central venous pressure
- Fall in heart rate
- Increased urine output
- Increase in mixed venous saturation
- Fall in base deficit
- Fall in blood lactate concentration

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Box 2 | Resuscitation end points in the study by Rivers and colleagues[6]

- Central venous pressure of 8-12 mm Hg
- Mean arterial pressure ≥65 mm Hg
- Urine output ≥0.5 ml/kg/hr
- Central venous oxygen saturation ≥70%

such as l-arginine and omega-3 fatty acids, actually increase mortality in patients with severe sepsis.[13] Interpretation of these studies is confounded by the effect of hyperglycaemia. The combination of glycogenolysis and insulin resistance means that hyperglycaemia is common in patients with sepsis and is associated with a poorer outcome.[14] Tight glycaemic control has been shown to reduce morbidity and mortality in a prospective randomised controlled trial in surgical patients.[15] A similar study in non-surgical patients resulted in a reduction only in morbidity.[16] We clearly need a more definitive understanding of the impact of hyperglycaemia and insulin treatment in patients with severe sepsis, which will hopefully be provided by an ongoing randomised controlled trial.[17]

What specific treatments are available?

Antimicrobials

First and foremost among specific treatments are prompt appropriate empirical antimicrobials. Treatment within four hours of admission reduces mortality and length of stay.[18] Delay in hypotensive patients increases mortality by 7.6% an hour.[19] Since the late 1980s, Gram positive organisms have replaced Gram negative ones as the most common bacteria causing sepsis. Retrospectively, around 20% of infections originate from each of respiratory, intra-abdominal, and urinary tract sources. However, at presentation, the source of infection is often unknown. Antibiotic treatment must be guided by the patient's susceptibility group (table) and local knowledge of bacterial resistance. Broad spectrum β lactam antibiotics would be the usual first line agent. If methicillin resistant *Staphylococcus aureus* is a risk, empirical vancomycin should be added. In the presence of risk factors for fungal infection, an antifungal agent may be prescribed initially or within 48 hours if no improvement occurs; decisions are guided by clinical judgment and the severity of the condition, ideally in consultation with infectious disease or microbiology colleagues. The importance of wide cover is illustrated by the much poorer prognosis in patients in whom the first line drugs are ineffective.[20] If strong clues to the source of infection exist, targeted narrower spectrum treatment is probably justified.

Protein C is synthesised by the liver and activated by thrombomodulin-bound thrombin, acquiring anti-inflammatory, antithrombotic, and anticoagulant effects. A recombinant human protein (drotrecogin alfa (activated)) was evaluated in a large prospective randomised controlled trial.[21] It was, somewhat controversially, approved in November 2001 by the US Food and Drug Administration on the basis of a reduction in the absolute risk of death of 6.1% (P=0.005) and subgroup analysis of predefined high risk patients (defined as an acute physiology and chronic health evaluation II (APACHE II) score of ≥25). In the intervening time two further randomised controlled trials have been published, one in children and the other in adults at low risk of death.[22,23] Both were stopped early on grounds of inefficacy. In addition, the calculated risk of serious haemorrhage from drotrecogin alfa (activated) has increased progressively with accumulating clinical experience. Overall, whether the risks of drotrecogin alfa (activated) outweigh the benefits is now far from clear, even in patients with a high risk of death.

Corticosteroids

Deficiency of adrenal steroid production in severe sepsis was originally described as acute haemorrhagic necrosis of the adrenal glands precipitating addisonian crisis and death—the Waterhouse-Friderichsen syndrome. High dose corticosteroid treatment in severe sepsis was initially investigated as an anti-inflammatory treatment and found to be of no benefit. Attention has now returned to the problem of adrenal insufficiency in severe sepsis. Complete adrenal failure is rare, but relative adrenal insufficiency is much more common, although the incidence depends on the definition used. In one study, for example, which defined adrenal insufficiency as a cortisol increment of ≤248 nmol/l (9 μg/dl) 30-60 minutes after 0.25 mg of tetracosactrin, 54% of the patients with septic shock met the criteria.[24] Two recent meta-analyses suggest that low dose hydrocortisone for five to 11 days in unselected patients with severe sepsis or septic shock significantly reduces both the duration of shock and in-hospital mortality, without incurring additional complications. The positive effect of low dose steroid replacement treatment may be even greater if it is restricted to patients selected on the basis of proved adrenal insufficiency.

Immunoglobulins and statins

Other therapeutic approaches deserve further investigation. Of these, intravenous immunoglobulin and statins are nearest to clinical evaluation. Intravenous immunoglobulin is not without adverse effects, which vary from hypotensive reactions to aseptic meningitis. Most of the infused antibody will not be specific for the organism

Patients' susceptibilities and implications for treatment

Susceptibility	Consider
In hospital or other institution	Resistant organisms, especially methicillin resistant *Staphylococcus aureus* (MRSA) and extended spectrum β lactamase producing Gram negative enteric organisms
Splenectomy	Capsulated bacteria, especially *Streptococcus pneumoniae*
School, university, or military	*Neisseria meningitidis*
Intravascular catheter	Staphylococci
Intubation and ventilation	Gram negative enteric organisms, pseudomonads, MRSA, Candida
Pharmacologically immunosuppressed	*Pneumocystis jirovecii*, cytomegalovirus, *Candida* spp, *Arpergillus* spp, *Nocardia* spp
Foreign travel	Malaria, legionella
Potential exposure to rat urine	Leptospirosis
Very young or very old	*Listeria monocytogenes*

SOURCES AND SELECTION CRITERIA

We searched Medline with the search phrase "((sepsis[title] OR septic*[title]) NOT (infant* OR neonat* OR child*))" and restricted the search to articles published in English in the previous three years. We individually reviewed the titles of the 2620 articles retrieved to identify major themes. Where necessary, we made additional searches based on key words or concepts that had been identified in the initial search. We also searched the Cochrane Library and Clinical Evidence. We then each used this information supplemented by knowledge and experience from our own field to prepare a brief review of the sections with which we were most familiar

responsible for the infection. The hope that polyclonal antiendotoxin antibody cross reactivity will be of use persists, despite the convincing failure of monoclonal antiendotoxin antibody to influence outcome. Several trials and analyses of these trials are in the literature, and both bodies of work have examples of conflicting or ambiguous results. One meta-analysis that separated trials into high and low quality studies showed no benefits in the high quality studies but a relative risk of death of 0.61 in the low quality studies. The authors conclude that the evidence from the high quality studies is enough to dissuade them from using intravenous immunoglobulin in sepsis except in randomised trials.[25] A larger review shows a relative risk of death of 0.91 in patients treated with polyclonal immunoglobulin. It concludes that polyclonal immunoglobulin G is promising but unproved.[26]

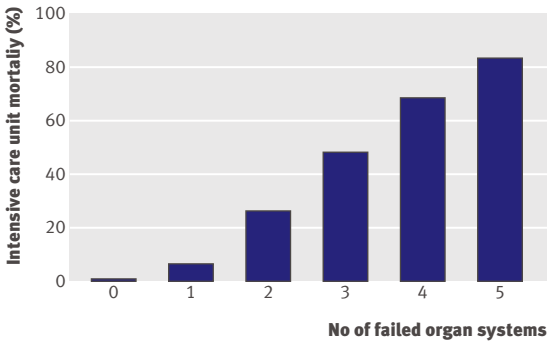
Statins are lipid lowering agents that act by inhibiting hepatic hydroxymethyl glutaryl coenzyme A reductase and are in widespread use for the prevention of coronary artery disease. Recognised as having anti-inflammatory properties, among many others, they have subsequently been shown to reduce the risk of developing sepsis, as well as the severity of and mortality from sepsis. Intriguingly, in a murine model of sepsis, treatment with statins instituted after the septic insult was able to prolong survival.[27] Whether this effect could be replicated in patients is not clear.

HMGB-1

Among the inflammatory response mediators being targeted, high mobility group box 1 (HMGB-1) protein is of particular interest. HMGB-1 is an essential nuclear DNA binding protein that acts as an "architectural" transcriptional cofactor. Secreted HMGB-1 is a potent inflammatory mediator that appears late in the septic cascade. It has several actions, including increased expression of a distinct gene set including those for inflammatory cytokines. Injection of recombinant HMGB-1 replicates the clinical features of sepsis in mice, including multiple organ failure and death. Conversely, antagonism of HMGB-1 in a rodent model of sepsis reduces organ damage and improves survival, even when treatment is started after the septic insult. Circulating concentrations of HMGB-1 are significantly increased in patients with severe infection and are lower in survivors than in non-survivors.[28] Two very different interventions seem to usefully reduce release of HMGB-1. Firstly, ethyl pyruvate, a stable aliphatic ester of pyruvate, effects a dose dependent reduction in HMGB-1 concentration and reduces mortality in a murine model of indolent sepsis, even when given 24 hours after its onset. Ethyl pyruvate has already been investigated in phase 1 studies in man. Secondly, release is inhibited by agonists of the α7-nicotinic acetylcholine receptor expressed on the surface of human macrophages, whose natural ligand is acetylcholine released from nerve endings of the common coeliac branch of the vagus nerve within the spleen. This represents the effector arm of the "cholinergic anti-inflammatory pathway" and suggests intriguing therapeutic possibilities not only for pharmacological intervention using synthetic agonists but perhaps even for psychological and biofeedback manipulation of the inflammatory response.

TIPS FOR NON-SPECIALISTS

- A favourable outcome is very dependent on early diagnosis and prompt treatment
- Appropriate samples for microbiological examination should precede antibiotic treatment, providing that this does not delay treatment
- Early, broad spectrum, empirical intravenous antimicrobial treatment and aggressive circulatory support are the mainstays of management



Relation between organ failure and intensive care unit outcome[31]

Multiple system organ failure and outcome

Until the progression of the septic process has been brought under control with effective antimicrobials and, where necessary, surgery, patients are at risk of sequential organ failure (box 3). Mortality is strongly associated with the number of failed organs (figure). In the medium term and long term, the only organs that show obvious residual dysfunction are the kidneys. Of patients who develop acute renal failure, less than 20% need dialysis on discharge from hospital and more than 50% of these eventually become independent of dialysis. The literature describing the medium term and long term quality of life of survivors is sparse, includes few patients, and is generally of poor quality. In one study, almost 50% of survivors had failed to return to their usual activities six months after discharge from intensive care[29]; even after 16 months, survivors were significantly less well than age matched controls.[30]

Box 3 | Common sequence of organ failure

Primary involvement
- Heart and circulation

Secondary involvement
- Kidneys
- Respiratory system
- Brain (often overlooked in younger patients)

Tertiary involvement
- Liver
- Haemostatic system

ADDITIONAL EDUCATIONAL RESOURCES

European Society of Intensive Care Medicine (www.esicm.org)—Access to a range of guidelines, including the surviving sepsis campaign guidelines for the management of severe sepsis and septic shock

Society of Critical Care Medicine (www.sccm.org/SCCM/LearnICU/Quick+Links)—Access to a range of guidelines

American Thoracic Society (www.thoracic.org/sections/clinical-information/critical-care/evidence-based-critical-care)—Useful information and access to guidelines

Information resources for patients

Meningitis Research Foundation (www.meningitis.org)—A UK based charity aimed at supporting research into meningitis and septicaemia, as well as providing education and awareness to reduce death and disability and give support to people affected

Intensive Care Society (www.ics.ac.uk/patrel/patrel.asp)—For information about many aspects of intensive care that might be of interest to the friends and family of a patient with septicaemia

Society of Critical Care Medicine (www.myicucare.org/sccm/MyICUCare)—For information that is relevant to patients in the United States

Conclusion

The severity of sepsis, its heterogeneous causation, the urgency of treatment, and the high mortality make it a problem area for randomised placebo controlled clinical trials, although the area is in striking need of these, particularly with newer biological therapeutic agents appearing. Meta-analysis and clinical experience are left to guide us through current therapeutic controversies. All of these, however, are of little use without a high index of clinical suspicion and the ability to act without delay when sepsis threatens.

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SUMMARY POINTS

A favourable outcome depends on early, aggressive, treatment

Antimicrobial treatment must take into account both patient susceptibilities and local resistance patterns; advice from infectious disease or microbiology colleagues is often helpful

Volume resuscitation and cardiovascular support should be titrated to simple clinical end points

Subtle signs of organ hypoperfusion should be sought in physically robust patients

The role of activated protein C and low dose steroids remains to be clarified