Intensive care medicine

Edited by Dr Simon V Baudouin MD FRCP,
Senior Lecturer in Anaesthesia and Critical Care Medicine,
University of Newcastle

Clinical trials in sepsis

David Saunders MBBS FRCA, Research Fellow in Critical Care Medicine

Simon V Baudouin MD FRCP, Senior Lecturer in Critical Care Medicine and Consultant Physician

The Royal Victoria Infirmary, Newcastle upon Tyne

Clin Med 2005;**5**:431–4

Epidemiology

Sepsis is an increasing and major healthcare problem worldwide.[1] Using data from 91 intensive care units (ICUs) collected between 1995 and 2000, there were estimated to be 51 cases of severe sepsis per 100,000 population in England, Wales and Northern Ireland over this period.[2] It was also reported that 27% of all admissions to critical care suffered from severe sepsis within the first 24 hours. There was 47% hospital mortality among these patients and they occupied 45% of total hospital critical care bed-days. The incidence of sepsis also appears to be increasing: there has been a 53% increase in the UK between 1996–1997 and 2001–2002.[3]

Pathophysiology

The reductionist approach taken by the cell and molecular biology research community has led to an enormous increase in the understanding of the basic science of sepsis.[1,4] However, as this review will indicate, translation of this knowledge into improved patient outcomes has proved allusive.

Sepsis is a result of a damaging host response to invasive infection.[5] As sepsis progresses to a stage of shock, there is a rapid development of multiple organ failure, including respiratory, renal, circulatory and neurological. The initiator of diffuse organ damage appears to be an intense and possibly dysregulated activation of the innate immune system. Several key features of activation are recognised (Fig 1):

1 The innate immune system recognises host microbiological invasion by binding microbiological products to a small number of 'pattern recognition' receptors present both on circulating leukocytes and on static interfaces (endothelial and epithelial).[6] These include the Toll-like receptor (TLR) family, one of whose members (TLR-4) binds to endotoxin. The potential importance of these receptors in sepsis is demonstrated by the resistance to lethal endotoxic shock of certain strains of mice with a naturally-occurring inactive mutation of TLR-4. In man, there is some evidence that outcome in sepsis is influenced by the possession of certain genetic variations of the TLR-4 receptor (so-called polymorphisms).
2 Recognition of microbiological invasion by host cells leads to a complex pro- and anti-inflammatory response. Macrophages probably play a key role in amplifying the pro-inflammatory signal by releasing several mediator molecules, including tumour necrosis factor (TNF), various interleukins and lipid compounds. Some of these mediators recruit additional cells, including neutrophils, to sites of infection/tissue injury.
3 The vascular endothelium is of central importance in sepsis.[7] Endothelial activation and damage occurs, which may in part explain the altered vascular responsiveness

Key Points

- **Sepsis is increasingly common in hospitalised patients, with a mortality exceeding 40%**
- **Patients with severe sepsis occupy approximately 45% of all critical care bed days in the UK**
- **Activation of the innate immune system, achieved by microbial pattern recognition receptors called Toll-like receptors, is a key step in the initiation of the sepsis syndrome**
- **Early, goal directed resuscitation of patients with severe sepsis improves outcome**
- **The stress-induced cortisol response is frequently abnormal in sepsis; low-dose 'physiological' steroid replacement is likely to improve outcome**
- **Treatment with recombinant activated protein C, a natural anticoagulant and anti-inflammatory agent, improves survival in severe sepsis**
- **Outcome in sepsis can be improved by the adoption of protocolised care, as reflected in the recently published Surviving Sepsis Campaign guidelines**

KEY WORDS: activated protein C, coagulopathy, outcome, randomised controlled trial, sepsis, shock, steroids

and vasodilated state characteristic of more advanced sepsis. Activated endothelial cells also release mediator substances, including the vasodilator nitric oxide.

4 The cellular and humoral response to severe infection leads to the release of naturally occurring cytopathic agents resulting in end-organ damage and failure.[8] Reactive oxygen species and their by-products have been detected in sepsis, in addition to the many cytokines and other circulating signalling molecules that cause cell necrosis or induce apoptosis.

The discovery of this early, intense pro-inflammatory response led to the development of the hypothesis that mortality in sepsis is the result of excessive innate immune system activation. The hypothesis was initially tested in experimental sepsis by blocking several inflammatory intermediaries, with apparent success.

Randomised clinical trials

1980–1990: the pre-molecular biology era

The inflammatory nature of sepsis led to a number of early investigations on the possible outcome benefit of corticosteroids. All these studies used pharmacological doses, often given for a relatively short period of time. The largest, involving 381 patients, reported an increased risk with steroid treatment, although confidence intervals crossed the no effect line. Meta-analyses of all high-dose trials of steroids in sepsis confirmed a lack of benefit or even harm.[9]

Recent renewed interest in steroids in the treatment of sepsis followed reports of relative adrenal suppression, as indicated by abnormal short Synacthen tests in patients with poor outcomes. A meta-analysis of several randomised controlled trials (RCTs) in which septic patients received lower physiological dose steroids for 5–7 days found a significant survival benefit with these lower doses.[9]

1990–2000: the molecular biology era

The ability to manufacture recombinant proteins and create monoclonal antibodies with therapeutic potential led to over 40 large RCTs in sepsis during the decade 1990–2000. Almost all were based on the hypothesis that blocking the host's inflammatory response would lead to a better outcome. However, these studies were either unsuccessful or, in a few cases, harmful to the intervention group.[10]

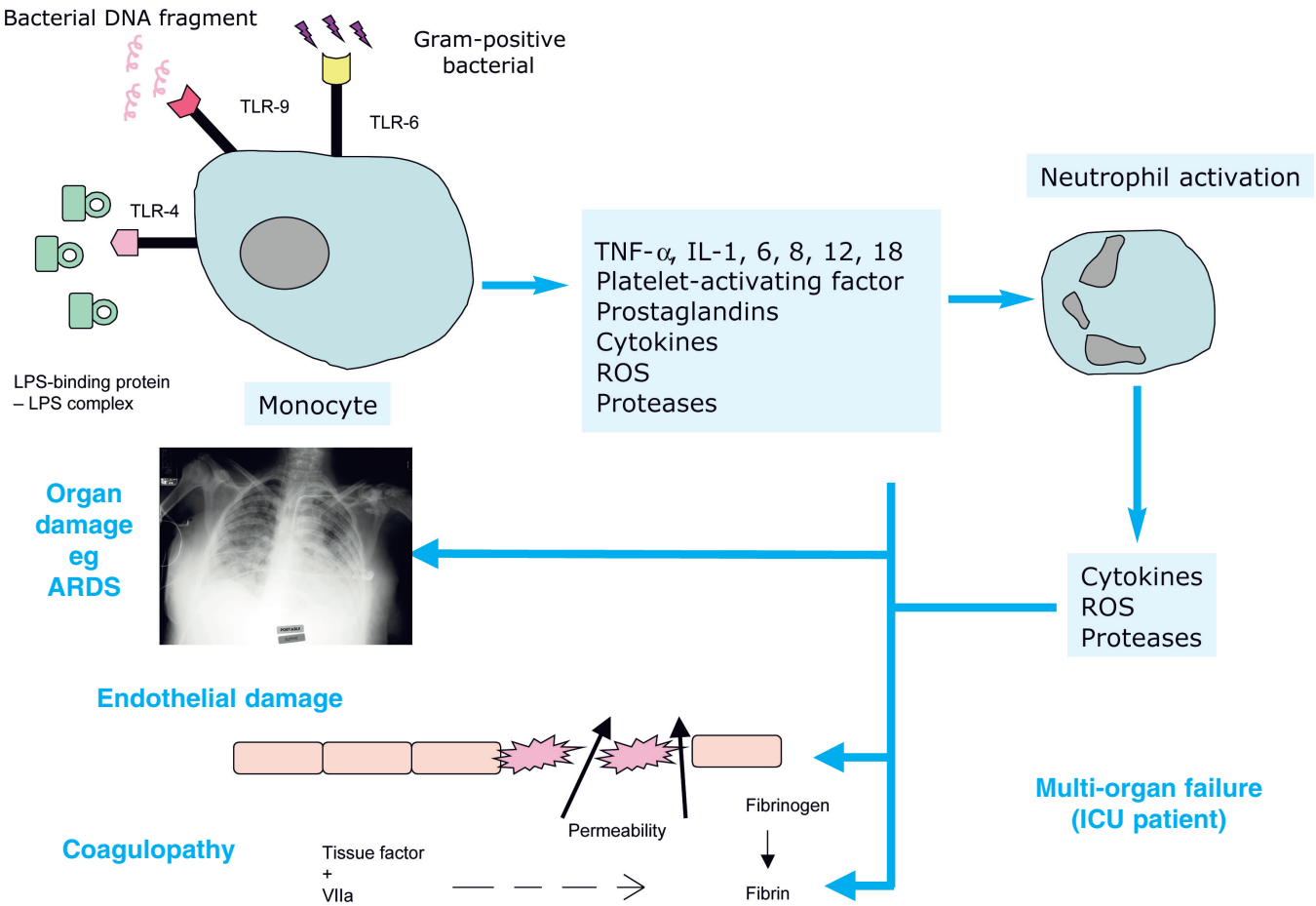

Fig 1. Key features of intense and possibly dysregulated activation of the innate immune system responsible for the initiation of diffuse organ damage (ARDS = adult respiratory distress syndrome; IL = interleukin; ICU = intensive care unit; LPS = lipopolysaccharide; ROS = reactive oxygen species; TLR = Toll-like receptor; TNF = tumour necrosis factor).

A large, multicentre anti-endotoxin antibody (Centoxin) trial provides an interesting case study. Initially reported as having a positive effect on survival in sepsis, it received a European product licence; this was subsequently revoked when further examination of the trial data by the US Food and Drugs Administration revealed inconsistencies in the trial design and analysis.[11]

Sepsis trials in the 21st century

Natural anticoagulants. Coagulation disturbances are probably a universal occurrence in sepsis (Table 1).[12] Healthy volunteers given subclinical doses of endotoxin or TNF show activation of both pro- and anticoagulant systems. The most striking coagulation problem in sepsis is disseminated intravascular coagulation, but more subtle abnormalities have recently been recognised. These include raised levels of the major initiator of coagulation, tissue factor (TF), and low levels of factor VII, indicating consumption of coagulation factors. The natural anticoagulant system is also activated, with reduced circulatory levels of antithrombin and protein C (PC) and increases in TF pathway inhibitor (TFPI). A correlation between the levels of these circulating anticoagulants and outcome in sepsis was reported in a number of studies.

The ability to manufacture recombinant versions of natural anticoagulants led to several successful Phase I and II studies and ultimately three large, multicentre Phase III studies (Table 2).[13–15] Only one,[14] which used recombinant activated PC (aPC), showed a significant survival benefit at 28 days in the treatment arm. In all the trials, the intervention group had an excess risk of serious bleeding. On the basis of the PROWESS trial,[14] aPC has been granted both a North American and European product licence for use in severe sepsis. However, its adoption into routine intensive care unit (ICU) practice has been slow because of remaining concerns about both the trial and the drug. These include:

- alteration in trial protocols during the study
- an apparent lack of effect in subgroups with lower severity of illness scores
- the potential for bleeding with treatment
- the cost.

In addition, although more recent one- and two-year follow-up data confirmed better in-hospital outcomes in the treatment group, there was no significant difference in outcomes at 3, 6, 12 or 24 months.[16] However, an *a priori* subgroup analysis still indicated benefit in sicker patients.

Table 1. Typical laboratory findings in the coagulopathy of sepsis and disseminated intravascular coagulation.

Laboratory investigation	Typical result
Activated partial thromboplastin time	Elevated
Prothrombin time	Elevated
Platelet count	Reduced
Fibrinogen	Reduced
Fibrin degradation products	Elevated
D-dimers	Elevated
Protein C	Reduced
Antithrombin	Reduced

Resuscitation

The failure of new pharmacological agents to influence outcome in severe sepsis has prompted some investigators to re-examine the early phase of care delivery. In a landmark study, Rivers and colleagues[17] randomised 263 patients admitted with severe sepsis via an urban emergency department into standard or haemodynamic goal-directed treatment. The principal difference in the intervention group was the use of central venous oxygen tension measurements to guide resuscitation. A highly significant difference in hospital mortality was reported in favour of goal-directed therapy (46.5% *vs* 30.5%). The cause of this difference was multifactorial, but both the speed of resuscitation and total fluid volume received by the intervention group were significantly greater. The study demonstrated that marked improvements in outcome in sepsis can still be achieved by better use of existing treatments.

This view was further confirmed by two recent reports of the use of antibiotics in sepsis.[18,19] Both studies reported a better outcome in patients who received adequate empirical antibiotic treatment, with absolute reductions in mortality of 17–22%.

The future of clinical trials and treatment in sepsis

Despite the few recent 'positive' RCTs in sepsis, most of them have been disappointing in terms of outcome.[20] Several factors may explain these findings, including:

- the fact that sepsis is a syndrome, not a single disease

Table 2. Randomised clinical trials of natural anticoagulants in human sepsis.

Trial	Substance	Publication year	No. of patients	28-day mortality (%)			
				Intervention	Controls	Difference	95% confidence intervals
Kyber Sept[13]	Antithrombin III	2001	2,314	38.9	38.7	–0.2	–10.9–8.9
PROWESS[14]	Activated protein C	2001	1,690	24.7	30.8	6.1	1.9–10.4
OPTIMIST[15]	Tissue-factor pathway inhibitor	2003	1,754	34.2	33.9	–0.3	–11–10

Table 3. Key components of sepsis care from the Surviving Sepsis guidelines.[21,22]

- Prompt recognition of sepsis
- Rapid resuscitation ('ABC' approach), including goal-directed fluid and inotrope therapy
- Appropriate empirical antibiotics following cultures
- Search for source of sepsis
- Low-dose steroid therapy
- Activated protein C
- Glucose control to maintain level <8.3 mmol/l
- ICU sedation protocols
- Low tidal volume mechanical ventilation
- Deep vein thrombosis prophylaxis
- Stress ulcer prophylaxis

ICU = intensive care unit.

- the lack of homogeneity in the patient population
- the varying host response to different infections, and
- the natural genetic variation in the host innate immune system and response to infection.

There is good evidence that patient outcomes can be improved by following standardised clinical pathways. This is reflected in the development of 'surviving sepsis' guidelines endorsed by major critical care organisations internationally.[21,22] These consist of a package of evidence-based (some supported by more evidence than others!) guidelines (Table 3), now being widely adopted by the critical care community.

There is no shortage of potential therapeutic targets in sepsis and further clinical trials are being undertaken. However, the front-line clinician should focus mainly on the basic details of clinical care as it is in this process of 'quickly getting it right' that outcome can currently be improved.

References

1 Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. Review. *N Engl J Med* 2003;**348**:138–50.

2 Padkin A, Goldfrad C, Brady AR, Young D *et al.* Epidemiology of severe sepsis occurring in the first 24 hrs in intensive care units in England, Wales, and Northern Ireland. *Crit Care Med* 2003;**31**:2332–8.

3 Jarman B, Aylin P, Bottle A. Trends in admissions and deaths in English NHS hospitals. *BMJ* 2004;**328**:855.

4 Singer M, De Santis V, Vitale D, Jeffcoate W. Multiorgan failure is an adaptive, endocrine-mediated, metabolic response to overwhelming systemic inflammation. *Lancet* 2004;**364**:545–8.

5 Annane D, Bellissant E, Cavaillon JM. Septic shock. Review. *Lancet* 2005;**365**:63–78.

6 Iwasaki A, Medzhitov R. Toll-like receptor control of the adaptive immune responses. Review. *Nat Immunol* 2004;**5**:987–95.

7 Peters K, Unger RE, Brunner J, Kirkpatrick CJ. Molecular basis of endothelial dysfunction in sepsis. Review. *Cardiovasc Res* 2003; **60**:49–57.

8 Netea MG, van der Meer JW, van Deuren M, Kullberg BJ. Proinflammatory cytokines and sepsis syndrome: not enough, or too much of a good thing? Review. *Trends Immunol* 2003;**24**:254–8.

9 Minneci PC, Deans KJ, Banks SM, Eichacker PQ, Natanson C. Meta-analysis: the effect of steroids on survival and shock during sepsis depends on the dose. Review. *Ann Intern Med* 2004;**141**:47–56.

10 Freeman BD, Natanson C. Anti-inflammatory therapies in sepsis and septic shock. Review. *Expert Opin Investig Drugs* 2000;**9**: 1651–63.

11 Cross AS. Antiendotoxin antibodies: a dead end? *Ann Intern Med* 1994;**121**:58–60.

12 Amaral A, Opal SM, Vincent JL. Coagulation in sepsis. Review. *Intensive Care Med* 2004;**30**:1032–40.

13 Warren BL, Eid A, Singer P, Pillay SS *et al.* Caring for the critically ill patient. High-dose antithrombin III in severe sepsis: a randomized controlled trial. *JAMA* 2001; **286**:1869–78.

14 Bernard GR, Vincent JL, Laterre PF, LaRosa SP *et al.* Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001;**344**:699–709.

15 Abraham E, Reinhart K, Opal S, Demeyer I *et al.* Efficacy and safety of tifacogin (recombinant tissue factor pathway inhibitor) in severe sepsis: a randomized controlled trial. *JAMA* 2003;**290**:238–47.

16 Angus DC, Laterre PF, Helterbrand J, Ely EW *et al.* The effect of drotrecogin alfa (activated) on long-term survival after severe sepsis. *Crit Care Med* 2004;**32**:2199–206.

17 Rivers E, Nguyen B, Havstad S, Ressler J *et al.* Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;**345**:1368–77.

18 MacArthur RD, Miller M, Albertson T, Panacek E *et al.* Adequacy of early empiric antibiotic treatment and survival in severe sepsis: experience from the MONARCS trial. *Clin Infect Dis* 2004;**38**:284–8.

19 Garnacho-Montero J, Garcia-Garmendia JL, Barrero-Almodovar A, Jimenez-Jimenez FJ *et al.* Impact of adequate empirical antibiotic therapy on the outcome of patients admitted to the intensive care unit with sepsis. *Crit Care Med* 2003;**31**:2742–51.

20 Polderman KH, Girbes AR. Drug intervention trials in sepsis: divergent results. Review. *Lancet* 2004;**363**:1721–3.

21 Dellinger RP, Carlet JM, Masur H, Gerlach H *et al.* Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Review. *Crit Care Med* 2004; **32**:858–73.

22 Levy MM, Pronovost PJ, Dellinger RP, Townsend S *et al.* Sepsis change bundles: converting guidelines into meaningful change in behavior and clinical outcome. *Crit Care Med* 2004;**32**(11 Suppl):S595–7.