

# Current drug treatment of SEPSIS

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*This article discusses the current drug therapies in sepsis, concentrating on recombinant human activated protein C and steroids*

**S**epsis is defined as the systemic inflammatory response to infection. This response results from the action of endogenous mediators producing generalised inflammatory reactions in organs remote from the initial focus, leading to varying degrees of end-organ dysfunction. Sepsis is the most common cause of death in the intensive care unit (ICU). Patients with sepsis are not all equally ill. Sepsis is a continuum of injury response ranging from sepsis to septic shock to multiple organ dysfunction syndrome (MODS).

In 1991, a consensus conference produced definitions of sepsis and its adverse sequelae.<sup>1</sup> The term systemic inflammatory response syndrome (SIRS) defines the clinical manifestations of the widespread inflammation that results from a variety of insults, including infection, pancreatitis, trauma and burns. Sepsis was defined as the systemic inflammatory

response to a documented infection. Severe sepsis is associated with organ dysfunction, hypoperfusion or hypotension (after excluding other causes of hypotension). Septic shock refers to those patients who remain hypotensive despite adequate fluid resuscitation (fluid replacement) and who display perfusion abnormalities such as lactic acidosis, oliguria and acute alteration in mental state. MODS describes the presence of altered organ function such that haemostasis cannot be maintained without intervention.

The incidence of mortality varies with the severity of the disease. One study of 153 septic patients found that 51 per cent died before they were discharged from hospital. By one month after discharge, 56.2 per cent of patients had died, which increased to 68 per cent after six months. At one year after admission, the mortality was greater than 71 per cent.<sup>2</sup>

## STANDARD TREATMENT

**R**outine management of the septic patient includes use of suitable antibiotics, taking into account any positive

microbiological culture results, the likely source of infection and likely tissue uptake of the antibiotic.<sup>3</sup>

In septic shock, there is an imbalance between oxygen supply and demand, resulting in cellular and organ dysfunction.<sup>4</sup> Fluid resuscitation attempts to reverse hypotension, which generally refers to a mean arterial pressure below 65–70mmHg.

The choice of fluid is hotly debated: Europeans traditionally favour colloids, whereas North Americans prefer crystalloids. In the presence of a dilated, high output circulation, vasopressors, such as noradrenaline, are started if fluids fail to restore adequate arterial pressure and organ perfusion.

Noradrenaline preferentially acts on the  $\alpha_1$ -adrenoreceptor, thereby causing vasoconstriction, which leads to an increase in systemic vascular resistance. Myocardial depression is also a common sequela of sepsis and it can lead to a low cardiac output (that is, less than 4L per minute). An inotrope, eg, adrenaline or dobutamine, is more appropriate in myocardial depression.

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## MONOCLONAL ANTIBODIES

The only product licensed for septicaemia used to be HA-1A, a human monoclonal antibody against endotoxin, marketed as Centoxin, which was withdrawn in 1993.<sup>5</sup> The licence followed publication of a trial by Ziegler *et al*<sup>6</sup> which compared HA-1A with placebo in 543 patients with presumed Gram-negative septicaemia.

Although no difference in survival was seen, a retrospective sub-group analysis of 200 of these patients with culture-proven Gram-negative septicaemia reported a significant reduction in mortality in the HA-1A group (51 per cent, HA-1A, versus 68 per cent, placebo). However, in Gram-positive, Gram-negative or fungal cultures, the mortality was higher for the HA-1A treated group (45 per cent, HA-1A, versus 40 per cent, placebo). The drug was voluntarily withdrawn, following an interim analysis of a further phase III trial which showed lack of benefit, as it became clear that it would be necessary to delay instituting HA-1A treatment until a bacterial diagnosis was present, making the treatment impractical. This experience with Centoxin has served to warn against over-reliance on retrospective sub-group analysis when the main benefits are not seen.

## STEROIDS

The evidence for the use of steroids in the treatment of septic shock has gone round full circle in the past 20 years, with recent interest focusing on low doses. The immune system is stimulated in infection. This stimulation is usually advantageous but in septic shock it becomes uncontrolled and excessive. Steroids modify the immune system in several ways that can be helpful in septic shock. They also inhibit macrophage and endothelial function. Steroids inhibit the migration of leucocytes to inflammatory sites and inhibit the adhesion of neutrophils to endothelial cells and the subsequent production of humoral factors. In addition to their anti-inflammatory effects, steroids also increase cardiac output and increase blood pressure by inhibiting nitric oxide synthesis. Corticosteroids also treat "relative" adrenal insufficiency and potentiate adrenergic receptivity.<sup>7</sup>

The first studies of steroids in sepsis investigated the use of high doses (30mg per kg methylprednisolone) for one to two days. Initially, the results in humans were positive.<sup>8</sup> However, there were two subsequent, well-designed double-blind, randomised, multicentre studies that failed to demonstrate any reduction in mortality.<sup>9,10</sup> Two meta-analyses concluded that steroids were either harmful<sup>11</sup> or ineffective.<sup>12</sup> These data discouraged the use of steroids in sepsis.

However, interest in steroids has been renewed by studies that have used lower doses of corticosteroids. A randomised double-

blind placebo-controlled study looked at 41 septic shock patients who required more than two days of catecholamines.<sup>13</sup> The steroid regimen was intravenous hydrocortisone 100mg three times daily for five or more days, which is then subsequently tailed off over six days. One-month mortality was 32 per cent for the treatment group and 63 per cent for placebo ( $P=0.045$ ; number needed to treat, NNT=3.2). Shock reversal was achieved at seven days in 68 per cent of the hydrocortisone group and 21 per cent of the placebo group ( $P=0.007$ ).

A different regimen was used by Briegel.<sup>14</sup> In this double-blind, single-centre study, 40 patients in septic shock were randomised to receive placebo or hydrocortisone (loading dose of 100mg followed by a continuous infusion of 0.18mg per kg per hour). On reversal of septic shock, the hydrocortisone dose was reduced to 0.08mg per kg per hour for six days, then tapered by 24mg per day. The major difference was seen in the time to reversal of vasopressor support. This was achieved in a median of two days with hydrocortisone and seven days in the placebo group ( $P=0.005$ ).

A randomised, multi-centre, placebo-controlled study of 299 septic shock patients was recently conducted in France.<sup>15</sup> The steroid regimen here was intravenous hydrocortisone 50mg four times per day plus oral fludrocortisone 50mg daily, initiated within eight hours of the onset of shock and continued for seven days. Fludrocortisone was added because the investigators had previously noted that about 40 per cent of patients with septic shock have low aldosterone levels, and it was considered that hydrocortisone alone would not be sufficient to replace this apparent mineralocorticoid deficiency. A 30 per cent reduction in mortality was seen at one month. The benefit occurred in those patients having a subnormal response to a short Synacthen test whereas those with a normal response showed a tendency toward harm. In the Synacthen test, tetracosactide (Synacthen), a synthetic analogue of corticotropin, is given to stimulate adrenal cortisol production. A responder to the Synacthen test will produce a rise in cortisol levels that will help to exclude primary adrenal failure.

There is an ongoing debate on the applicability of the Synacthen test to intensive care. Critics of the test point out that, in the critically ill patient, there is significant variation of the test result in the same patient at different times of the day. Furthermore, cortisol is 95 per cent bound to cortisol-binding globulin (CBG): CBG concentrations can be increased or decreased in critical illness and is affected by acidosis. However, it has been demonstrated that, in septic shock, the addition of hydrocortisone to those not responding to the Synacthen test restores their response to noradrenaline (an increase in blood pressure) and improves mortality.<sup>15</sup>

A large European steroid study (CORTICUS) with many similarities to the French study will soon commence, but with some important differences: patients will be eligible for recruitment within 24 hours of sepsis rather than eight hours. Also, fludrocortisone will not be part of the steroid regimen which will consist of intravenous hydrocortisone 50mg four times daily for seven days, then tailed off over a week.

## ANTI-TNF ANTIBODY

Over the past 10 years, there have been a cluster of trials investigating anti-tumour necrosis factor (TNF) effects in sepsis. Interpretation has been made difficult by the variety of products used, all with differing regimens and patient groups. The key trials have been summarised in Table 1, p99. The most impressive results are seen in the yet to be published MONARCS study,<sup>16</sup> where a statistically significant absolute reduction in mortality of 3.5 per cent was seen at 28 days.

A recent editorial<sup>24</sup> commented that anti-TNF therapy is likely to have a better safety profile than recombinant human activated protein C (rhAPC) in patients who are at risk of haemorrhage. However, it was observed that prolonged anti-TNF therapy has been associated with increased infection in patients with rheumatoid arthritis.

## TFPI

Tissue factor pathway inhibitor (TFPI) is a naturally occurring anticoagulant and anti-inflammatory protein. It inhibits the procoagulant effects of tissue factor by binding to the tissue factor-factor VIIa complex. A phase II study of TFPI reported a trend towards clinical benefit.<sup>25</sup> A larger phase III study has recently been completed and the results of the trial, though not yet in the public domain, are reported to have had no major impact on reducing mortality.

## rhAPC

Sepsis has been described in terms of an inflammation-coagulation loop in which both processes amplify each other, eventually leading to vascular collapse, organ failure, thrombosis, ischaemia, free radical damage, and finally, death.<sup>26</sup>

Activated protein C (APC) is an endogenous anticoagulant protein with anti-inflammatory and pro-fibrinolytic properties. Protein C, the zymogen or inactive precursor, is converted to the active form APC by thrombin bound to thrombomodulin, an endothelial membrane protein. APC may interfere with the amplification loops modulating both inflammation and coagulation. Many septic patients have low APC levels, partly because APC is used up

Table 1: Key trials involving anti-TNF therapy

Trial	Anti-TNF product	Patient group	Number of patients	Results
NORASEPT I <sup>17</sup>	Immunoglobulin G (IgG) monoclonal antibody	Sepsis and severe septic shock	994	No overall benefit compared with placebo. In septic shock, a reduction of septic shock was seen at two weeks. At 28 days, there was a 17 per cent relative reduction in mortality.
INTERSEPT <sup>18</sup>	As above	Septic shock	420	14.5 per cent relative reduction in mortality in the 3mg per kg group. No reduction in mortality seen in 15mg per kg group.
NORASEPT II <sup>19</sup>	Mural monoclonal anti-TNF-alpha 7.5mg per kg	Septic shock	1,900	No difference in mortality versus placebo.
Reinhart K <i>et al</i> <sup>20</sup>	Fragments of a murine IgG3 monoclonal antibody to TNF-alpha	Sepsis	122	No difference in mortality versus placebo.
Fisher C.J.Jr <i>et al</i> <sup>21</sup>	p55 TNF receptor protein construct dose-ranging study	Septic shock with or without organ dysfunction	141	Dose-dependent increase in mortality. Mortality 30 per cent in the placebo group and 53 per cent in the 1.5mg per kg group.
Abraham E <i>et al</i> <sup>22</sup>	p55 TNF receptor fusion protein	Severe sepsis with or without early septic shock	1,342	No improvement in mortality at 28 days.
RAMSES <sup>23</sup>	Afelimomab anti-TNF-alpha monoclonal antibody	Septic patients with interleukin (IL)-6 > 1,000 picogram per ml	446	No difference in mortality detected.
MONARCS <sup>16</sup>	Afelimomab	Severe sepsis	2,534	Mortality 32.3 per cent in treatment group and 35.9 per cent in placebo $P=0.049$ NNT 28. Also reduction in organ dysfunction and IL-6 levels.

in sepsis and partly due to inflammatory cytokines down-regulating thrombomodulin and the endothelial cell protein C receptor. These components of the coagulation system are needed to convert the inactive protein C to the activated form. In addition, APC inhibits activated factors VIII and V which leads to a reduction in thrombin formation. Furthermore, APC stimulates fibrinolysis by lowering the concentration of plasminogen-activator inhibitor type 1. Panel 1 summarises the actions of rhAPC.

The PROWESS<sup>27</sup> study was a placebo-controlled double-blind trial that investigated the efficacy and safety of rhAPC in severe sepsis in 1,690 subjects. The active group received rhAPC as drotrecogin-alfa activated 24mg per kg per hour for 96 hours. The inclusion criteria were a known or suspected infection, three or more signs of systemic inflammation within a 24-hour period, and sepsis-induced dysfunction of at least one organ or system lasting no longer than 24 hours (see Panel 2, p100).

The trial was stopped early because an interim analysis favoured the rhAPC group. At 28 days, the mortality was 30.8 per cent in the placebo group compared with 24.7 per cent in the rhAPC group ( $P=0.005$ ; NNT=16). Decreases were seen in serum IL-6 levels to a greater extent in the rhAPC group on days 1, 4, 5, 6, and 7. Despite excluding patients from the trial if they had a high bleeding risk, there was more serious

bleeding in the rhAPC group (3.5 per cent versus 2 per cent,  $P=0.06$ ), which occurred mainly during the infusion phase. There was no significant difference between the groups in terms of time on the intensive care unit, time in hospital, or time spent on a ventilator.

The study raises some important questions, such as whether the 28-day mortality improvement translates into a longer-term benefit. Other questions that were raised include:

- 1 Does early administration of rhAPC make a difference?
- 1 Do some patients require more rhAPC, others less?
- 1 Can the NHS afford to treat all patients who meet the entry criteria?
- 1 Should rhAPC be used in patient groups who were excluded from the trial, eg, children?

Although not addressed in the PROWESS study, there has been interest in sub-group analyses in order to identify those patient groups who could benefit most. It appears that those with three or more failing organs and those with shock benefited much more from rhAPC. However, these findings must be treated with caution because the groups were not matched for analysis, nor was this a predetermined study endpoint.

The suitability and implications of applying the PROWESS study to the UK model

has been investigated with the Intensive Care National Audit and Research Centre (ICNARC) database.<sup>28</sup> Based on data collected in 67 per cent of ICUs in England, Wales and Northern Ireland, it is reported that 28 per cent of all patients admitted to adult ICUs met the definition of severe sepsis used in the PROWESS study. The ICNARC-reported hospital mortality of 44.7 per cent was far higher than the 30.8 per cent in the control group at 28 days in the PROWESS trial. If only half of the 28 per cent of patients were treated with rhAPC in England and Wales, then the cost may be between £30–50m per year.

### Panel 1: Actions of rhAPC

Regulates coagulation: along with co-factor protein S, it inactivates factors Va and VIIIa, hence blocking thrombin generation

Regulates inflammation by

- 1 Impairing leucocyte attachment of selectins
- 1 Reducing cytokine release from monocytes
- 1 Blocking TNF-alpha release from leucocytes
- 1 Inhibits thrombin generation

Regulates fibrinolysis

## VASOPRESSIN

Endogenous vasopressin levels appear to be inappropriately low in sepsis, compared to the raised levels seen in other shock states, eg, cardiogenic shock and hypovolaemic shock. Several studies have evaluated the use of a low dose (0.01–0.04 units per minute) continuous infusion of vasopressin in septic shock patients resistant to fluids and noradrenaline.<sup>29–31</sup> Vasopressin had an effective pressor action in over 85 per cent of cases. However, a rebound hypotension occurred on discontinuation that necessitated the reinstatement of vasopressin or an increased requirement of noradrenaline.

Terlipressin is a long-acting synthetic analogue of vasopressin licensed for variceal haemorrhage. It has successfully been used at the UCL Hospitals in septic shock resistant to noradrenaline, steroid and methylene blue in a small series of patients.<sup>32</sup> The dose used was a 1–2mg bolus with the peak effect being seen after 20 minutes and lasting for four hours or longer.

### Panel 2: The PROWESS trial

#### Definition of severe sepsis used in the trial

Known or suspected infection

plus:

three or more of the following signs of systemic inflammation within 24 hours

- 1 Temperature 38C or 36C
- 1 Heart rate 90 beats per minute
- 1 Respiratory rate 20 breaths per minute or arterial carbon dioxide tension (PaCO<sub>2</sub>) 32mmHg or mechanical ventilation for an acute process
- 1 White cell count 12,000 per mm<sup>3</sup> or 4,000 per mm<sup>3</sup>

plus:

At least one sepsis-induced organ dysfunction lasting no longer than 24 hours

#### Key exclusion criteria used in the trial

Pregnancy or breast-feeding

Age <18 or weight >135kg

Platelet count <30,000 per mm<sup>3</sup>

Increased risk of bleeding

Known hypercoagulable condition

Human immunodeficiency virus infection

Chronic renal failure requiring dialysis (acute renal failure was not an exclusion criteria)

Imminent death or not expected to survive up to 28 days due to an intractable medical condition

Portal hypertension, jaundice, cirrhosis or chronic ascites

Acute pancreatitis without a source of infection

Drugs that increase bleeding risk, such as treatment-dose unfractionated heparin within eight hours, treatment-dose low molecular weight heparin within 12 hours, warfarin within seven days, aspirin at a dose higher than 650mg daily within three days, intravenous thrombolytic therapy within three days, glycoprotein IIb/IIIa inhibitors within seven days. Anti-thrombin III at a dose higher than 10,000U within 12 hours or protein C within 24 hours

## METHYLENE BLUE

Methylene blue can be useful in elevating blood pressure in resistant septic shock with a bolus dose of 2mg per kg over 15 minutes.<sup>33,34</sup> It acts by inhibiting guanylate cyclase. Nitric oxide (NO) is formed from L-arginine by nitric oxide synthases. NO stimulates soluble guanylate cyclase on vascular cells to produce both vascular relaxation and reduced responsiveness to catecholamines (hyporeactivity). Methylene blue inhibits this process, thus increasing the vascular tone.

Other drugs that have been investigated for use in severe sepsis are shown in Panel 3.

## CONCLUSION

Almost 60 randomised, controlled trials have been reported in sepsis, involving about 15,000 subjects. Most of these trials have failed to demonstrate any benefit and have cost over \$1bn to undertake.

There are a number of potential reasons for the lack of efficacy. Sepsis is a complex biological cascade that is still poorly understood.

The patient groups are not heterogeneous. The primary endpoint is often the 28-day mortality, but the patients often remain ill for longer, and short-term survival does not necessarily translate into long-term benefit. After several years of frustrating results, the new millennium has heralded some major breakthroughs.

Recombinant activated protein C (rhAPC) is about to be licensed for the treatment of severe sepsis and low dose steroids also appear to be effective. Vasopressin and terlipressin are promising agents in resistant septic shock. Funding rhAPC will present problems for the intensive care community and the health care commissioners.

Although many questions remain unanswered with rhAPC, its introduction will be seen as a major step forward in the treatment of sepsis. In the absence of a NICE review of rhAPC, there is likely to be a diverse

### Panel 3: Drugs that have been tested in severe sepsis

#### Anti-inflammatory drugs

Ibuprofen  
Prostaglandin E<sub>1</sub>  
Pentoxifylline

#### Oxygen scavengers

N-Acetylcysteine  
Selenium

#### Drugs enhancing host defences

Immunoglobulins  
Granulocyte stimulating factors  
Immunonutrition

#### Others

Growth hormone  
Ketoconazole  
Polymyxin B  
Taurolidine  
Antithrombin III

use of these products until co-ordinated guidelines are accepted.

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