Pharmacological treatment of sepsis

Armand R.J. Girbes*, Albert Beishuizen, Rob J.M. Strack van Schijndel

University Hospital VU Medical Centre, Amsterdam, The Netherlands

INTRODUCTION

Sepsis is defined as the combination of systemic inflammatory response syndrome (SIRS) and documented infection. SIRS is a relatively vague entity and refers to the presence of two or more of the following: (i) body temperature >38.5 °C or <35 °C; (ii) signs of respiratory distress (respiratory rate >20/min or arterial CO₂ tension <32 mmHg or need for mechanical ventilation); (iii) heart rate >90 beats/min; (iv) white blood count >12 000/mm³ or <4000 mm³ or immature forms >10%. In case of severe sepsis signs of organ failure are present, whereas in septic shock, hypotension with the need for pharmacological treatment exists. The incidence of sepsis is much higher than generally believed and amounts to 50–95 cases per 100 000 people per year. Furthermore, a yearly increase of 9% is noted. Severe sepsis and septic shock represent approximately 10% of all intensive care unit (ICU) admissions and sepsis is the third main cause of death, after chronic coronary disease and myocardial infarction, but before lung cancer or bowel cancer [1,2]. Mortality rate depends not only on multiple factors such as age, the occurrence of shock, causative organism, portal of entry, delay of initial treatment and adequacy of early empiric antibiotic treatment, but also on the type of ICU organization (intensivist driven or not, number of ICU nurses per patient) [3]. However, it is as high as 30–35% in clinical trials and up to 55% in epidemiological studies. Pharmacological treatment of (severe) sepsis is diverse and includes standard treatment in the ICU in terms of provision of comfort with (as little as possible) sedative agents, antimicrobial and vasoactive drugs, and optimal fluid management. The role of steroids remains ill-defined. Increased understanding of the mechanisms underlying the septic response – release of cytokines, diffuse endovascular injury and procoagulant host response – led to the testing of various drugs that were aimed at interrupting at various steps of the cascade. Of all these drugs tested, only drotrecogin alpha (activated protein C) proved to be effective in terms of survival in a single study [4]. However, source control, i.e. treatment aimed at the cause of sepsis, and early appropriate antibiotic treatment are the key for successful cure of the patient.

Keywords
dopamine, drotrecogin alpha, epinephrine, norepinephrine, protein C, sepsis, septic shock, shock, trial design

ABSTRACT

The incidence of sepsis, the combination of a systemic inflammatory response syndrome and documented infection, is as high as up to 95 cases per 100,000 people per year. The understanding of the pathophysiology of sepsis has much increased over the last 20 years. However, sepsis combined with shock is still associated with a high mortality rate varying from 35 to 55%. Causative treatment, source control and antibiotics started as soon as possible, are the cornerstone of therapy in combination with symptomatic treatment in the ICU. The pharmacological interventions, including fluid resuscitation, vasoactive drugs and adjunctive drugs such as steroids, activated protein C are discussed. The possible beneficial role of strict glucose control is also addressed. Since many drug intervention studies were negative, lessons should be learned from earlier experiences for future trials. Source control and level of intensive care should be eliminated as confounders.
In this review we address the symptomatic treatment of sepsis, including the use of vasoactive drugs and appropriate fluid resuscitation. The role of monitoring in the intensive care setting is briefly highlighted. Recent drug intervention trials in (severe) sepsis are discussed, including steroids and the use of insulin for tight glucose control. In addition, we discuss possible causes of failure of new drugs considered to be promising. Finally, we address the question as regards the lessons that can be learned from earlier experiences for future trials.

CAUSATIVE TREATMENT OF SEPSIS

Treatment of sepsis can be of two types: causative and symptomatic. As severe sepsis is a life-threatening state, the patient must be kept alive in order to win time for the causative treatment to be effective and to create circumstances for healing. Causative treatment, i.e. source control, depends of course on the cause of the sepsis. If the cause can be treated surgically, surgery remains the cornerstone of sepsis treatment, e.g. in case of an abdominal disaster like bowel perforation or severely infected necrotizing pancreatitis, surgical treatment is warranted. Antibiotics are also of great importance for treating both surgical and non-surgical cases of severe sepsis. The administration of the correct antibiotics and early timing improve survival rate in patients [5–7]. The choice of antibiotics depends on the suspected infection focus and local, geographic situation and data from microbial laboratories. For example, in the Netherlands methicillin-resistant Staphylococcus aureus (MRSA) is very rare, whereas in the southern European countries it is endemic. Therefore, in the Netherlands in case of a suspected S. aureus infection, no initial coverage against MRSA is deemed necessary, whereas in southern European countries this would be unthinkable [8].

SYMPTOMATIC TREATMENT OF SEVERE SEPSIS

Severe sepsis is accompanied by tissue hypoperfusion, related to reduced cardiac performance and cardiac function, and vasodilatation. Additionally, because of systemic inflammation and concomitant capillary leakage, fluid is lost from intravascular to extravascular regions. The ensuing relative and absolute hypovolemia and tissue hypoperfusion give rise to malfunction of hypoperfused organ systems. The initial treatment consists consequently of repletion of the underfilled vascular bed with fluids, the so-called ‘fluid resuscitation’.

FLUID RESUSCITATION

Intravenous infusion of fluids replenishes the vascular volume. Fine tuning of the amount and speed of infusion helps restore cardiac function by optimizing cardiac preload. The optimal cardiac preload in these circumstances is defined as the preload where additional fluid infusion or increase of filling pressures does not result in a further increase of cardiac output [9]. Although some guidelines advocate filling pressures aimed at a specific figure, e.g. a central venous pressure of 8–12 mmHg in the Surviving Sepsis Campaign (SSC), such a rule does not take into account the dynamic changes of the physiological properties of the heart during sepsis [10]. It is therefore better to monitor closely the effect of fluid infusion on parameters such as cardiac output, blood pressure, heart rate, urine output and blood lactate level and to decide on this basis whether further infusion of fluids would be of benefit. In the past, liberal fluid administration in sepsis was advocated, but over the last few years accumulating evidence suggests that a more or less restricted policy, especially in patients with accompanying acute lung injury, is advantageous in terms of shorter ICU stay [11]. So far, no differences in mortality have been shown related to fluid management strategies per se, nor to the choice of fluids. For fluid resuscitation the clinician can use artificial colloids, natural colloids (albumin) and crystalloids. Some remarks on the choice of fluids can be made. The SAFE study indicated that albumin is as safe and effective as crystalloids [12]. However, albumin is more expensive. No differences in terms of survival have been shown when comparing crystalloids and colloids, although administration of hydroxyl ethyl starches may increase the risk of acute renal failure [13]. The goals achieved by administration of fluids are more significant than when fluids, crystalloids or colloids (e.g. gelatins) are administered.

VASOACTIVE DRUGS IN SEPSIS

If fluid resuscitation fails to restore sufficient perfusion and perfusion pressure of all vital organs, vasoactive drugs must be used to re-establish these. Tuned pharmacological treatment aimed at correction of the circulatory abnormalities, next only to fluid management, is therefore required. It is evident that immediate treatment aimed at specific hemodynamic goals is life-saving [14]. Short-acting vasoactive drugs can be easily titrated, in terms of dose and choice, by the effect on circulatory and metabolic parameters. Direct circulatory parameters like
blood pressure, cardiac output, cardiac filling pressures, pulmonary artery pressures, volumetric echocardiographic dimensions, next to parameters of organ function like diuresis, and metabolic parameters like venous oxygen saturation and blood lactate levels, may guide treatment in the ICU. As vasodilation with resulting hypotension and insufficient perfusion pressure are prominent, vasoactive drugs with at least vasoconstrictive properties are used. Catecholamines such as dopamine, norepinephrine and epinephrine are among the most frequently used vasoactive drugs in the ICU for their vasoconstrictive, alpha-1 adrenoceptor-mediated activity (Table I). For long, the additional dopaminergic effect of dopamine was considered to preserve renal function and prevent renal failure, making it the first-choice catecholamine [15]. Data from the literature however, have not supported this presumption, albeit in some guidelines and local ICUs, dopamine is still used as the first-choice vasoactive drug for treating sepsis [16,17]. Norepinephrine seems a more logical choice in view of its potent vasoconstrictive effects, even where dopamine fails to raise perfusion pressure [18]. Despite the fact that norepinephrine induces peripheral vasoconstriction (because of alpha-1 receptor stimulation), cardiac output does not decrease. This relates to the beta-adrenergic inotropic effect of norepinephrine and an increase in coronary perfusion [19]. The latter may be related to an increase in induced coronary vasodilation and/or higher coronary perfusion pressure [20]. Norepinephrine can be combined with dobutamine, whenever additional inotropy is desired in case of myocardial dysfunction, related to the sepsis. Epinephrine is frequently used in the United Kingdom as a first-line vasoactive drug in sepsis, although in some small randomized trials epinephrine has shown deleterious effects on splanchnic blood flow and acid–base balance.

However, in a very recent randomized double-blind study, albeit in only 330 patients, no difference in efficacy and safety was observed between epinephrine alone and norepinephrine plus dobutamine [21]. Although vasopressin is capable of increasing blood pressure and reducing the need for norepinephrine, its role in sepsis remains unclear. Concerns about the adverse effects of vasopressin on coronary and splanchnic circulation make further studies necessary, before it becomes a standard of care in sepsis [22]. A very recent trial, comparing norepinephrine with vasopressin in patients with septic shock demonstrated no differences in survival outcome [23].

As all vasoactive drugs have potential side-effects, such as proarrhythmias and increased myocardial oxygen consumption, they should only be administered when necessary and according to the principle ‘enough is enough’. When hemodynamic goals, as mentioned above, have been achieved, the clinician should continuously look – after some time of ‘consolidation’ – for the possibility to slowly decrease the rate of infusion of vasoactive drugs. Continuously monitored data on blood pressure, heart rate, diuresis, central venous oxygen saturation and arterial blood gas, and data from the pulmonary artery catheter and that obtained echocardiographically, will guide the clinician intensivist to wean and change the vasoactive drugs as soon as possible.

**ADJUNCTIVE DRUG INTERVENTION TRIALS**

Since the late 1980s various drugs have been tested, aimed at specific steps in the septic cascade [4]. The first large randomized clinical trial (RCT) was published in 1991, evaluating the effect of an endotoxin-binding human monoclonal IgM antibody [24]. Even though initially seen by some as a positive study, it was in fact a negative study showing benefit only in a not previously defined subgroup. Later studies confirmed the lack of beneficial effect on survival in patients with sepsis. Although over 80 trials were performed in later years, testing various drugs, only one trial examining the effect of activated protein C (aPC) showed an improved outcome in terms of survival [25]. A universal pattern was found in all other trials: a specific single step in the cascade was considered very important, as indicated by studies of animal models and increased knowledge of the pathophysiology of sepsis. Then, promising phase II studies led relatively quickly to large phase III studies.

### Table I

<table>
<thead>
<tr>
<th>Catecholamine</th>
<th>DA1</th>
<th>DA2</th>
<th>alfa1</th>
<th>alfa2</th>
<th>beta1</th>
<th>beta2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dobutamine</td>
<td>0</td>
<td>0</td>
<td>0–1</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Dopamine</td>
<td>2</td>
<td>1</td>
<td>1–2</td>
<td>0–1</td>
<td>1–2</td>
<td>0–1</td>
</tr>
<tr>
<td>Dopexamine</td>
<td>1</td>
<td>0–1</td>
<td>0</td>
<td>0</td>
<td>0–1</td>
<td>2</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>0</td>
<td>2</td>
<td>1–2</td>
<td>1–2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td>0</td>
<td>2</td>
<td>1–2</td>
<td>1–2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Isoprenaline</td>
<td>0</td>
<td>0–1</td>
<td>0–1</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fenoldopam</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The number refers to the amount of receptor stimulation, with 0 = low and 2 = high.
without sufficient dose-finding studies. Many ICUs are involved in large multicenter studies and each ICU includes only a few patients. No specific criteria on the type, level or organization of the ICU are requested for participation. Concomitant treatment is in general ill-defined. Data on whether or not successful source control has been established are generally lacking. It is very unlikely that any adjunctive therapy can be effective if the source of infection is not sufficiently treated.

**ACTIVATED PROTEIN C (DROTRECOCIN ALPHA)**

In the course of sepsis, multiple cellular and biochemical pathways are activated, leading to the generation of proinflammatory mediators such as tumor necrosis factor, interleukin (IL)-1β, IL-6 and IL8. Lipopolysaccharide (LPS), a microbial product, and several proinflammatory cytokines increase the expression of procoagulant protein tissue factor in endothelial cells, monocytes and macrophages, which is associated with the activation of procoagulant pathways. This results in microvascular thrombosis and disseminated intravascular coagulopathy (DIC). This is in general accompanied by a decrease in the level of natural anticoagulants such as protein C, antithrombin and tissue factor pathway inhibitor (TFPI). The result is a predominant procoagulant and antifibrinolytic state. Lower levels of protein C are associated with an increased risk of death in patients with (severe) sepsis. In baboons, it had been shown that infusion of protein C reduced mortality from *Escherichia coli* injection.

The only successful phase III study so far in patients with severe sepsis is the PROWESS trial, published in 2001 [25]. In this prematurely terminated study, the effect of activated protein C (aPC or drotrecogin alpha) as an adjunctive therapy was tested in 1690 patients, instead of 2280 patients, as originally planned. A planned interim analysis revealed a 6.1% absolute mortality reduction. Although this study initiated the inclusion of aPC treatment in many national and international guidelines on the treatment of severe sepsis, some important concerns remain. First, only one – prematurely stopped – randomized clinical trial on efficacy is available. Secondly, although not mentioned in the original publication, halfway through the study some inclusion criteria were changed and it became clear that the efficacy of aPC was significantly lower in the first part of the study. The additional risk of severe bleeding was 1.5%. Subsequent additional studies of the same population revealed a sustained long-term effect on survival only in a predefined subgroup with an APACHE II score of >24. At this moment, a new RCT with aPC in patients with severe sepsis is foreseen. Other studies of aPC, including less severely ill patients with sepsis and in children with sepsis, failed to demonstrate a beneficial effect [26,27]. Randomized trials with other natural anticoagulant proteins, such as antithrombin III (ATIII) and TFPI failed to show an improved outcome [28]. It is of note that in the TFPI trial, initially favourable results disappeared after inclusion of more patients.

**CORTICOSTEROIDS**

The SSC recommends the treating of patients with a vasopressor-dependent septic shock with low-dose steroids [10]. The single available positive large RCT regarding this issue comprises a patient group with severe septic shock (systolic blood pressure <90 mmHg for at least 1 h, despite fluid replacement and vasopressor therapy) [29]. This trial showed no effect on mortality after 28 days in the whole study population, but only in a subgroup of non-responders to the ACTH stimulation test. The reliability of this test for the identification of relative adrenal insufficiency in patients with septic shock has been disputed, as the results of this test are poorly reproducible in these patients. Furthermore, instead of free cortisol, Annane et al. measured total cortisol, which can be falsely reduced because of the concomitant hypoalbuminemia in septic patients. When combining these data with those of smaller trials, the data suggested that corticosteroids reduce mortality [30]. However, a recently published study, unfortunately inadequately powered to detect a clinically important effect, did not show an improvement in survival or reversal of shock [31]. It remains therefore uncertain which septic patients benefit from corticosteroids.

**GLUCOSE CONTROL**

In 2001, van den Berghe et al. published the results of a study, demonstrating a clinically and statistically significant fall in mortality in patients under intensive care treated by intensive insulin therapy, aimed at attaining glucose levels between 4.4 and 6.1 mmol/L [32]. The intervention group was compared with a control group, where glucose level up to 12 mmol/L was accepted. The reduction in mortality was spectacular, with an absolute reduction of 3.7% (10.9% in the control group and 7.2%...
in the intervention group). In a subgroup of patients who remained more than 5 days in the ICU, the reduction was even more obvious: a mortality of 26.3% in the control group compared with 16.8% in the intervention group. An absolute reduction of almost 10% was therefore achieved. Besides the fact that a particular feeding protocol may have played a role in the results of this single-center study, the most important criticism was regarding the case-mix of the population studied: 63% cardiac surgery patients and only 5% non-surgical patients. In 2006 the same group from Leuven published a similar intervention trial in non-surgical patients [33]. In the total population, no effect of intensive insulin therapy on mortality could be detected. However, in the intensive insulin intervention group the risk of hypoglycemia (glucose <2.2 mmol/L) increased by a factor of 6 and hypoglycemia was recognized as an independent risk factor for mortality [34]. Intensive insulin therapy in septic patients was investigated by Brunkhorst et al. [35]. The study was stopped early because of safety reasons related to hypoglycemia in the insulin intervention group. However, it is not unreasonable to assume that glucose control to some extent may be beneficial, but one should be aware of the risks of hypoglycemia and levels of glucose that need to be attained should not be that low [36]. In the international directives for the treatment of severe sepsis, expert opinion recommendations are given for glucose control with levels <8.3 mmol/L, a little bit higher than that in the original studies [10].

**FUTURE DIRECTIVES AND PERSPECTIVES FOR PHARMACOLOGICAL TREATMENT OF SEPSIS**

A few RCTs are underway with various agents as mentioned in Table II. A large multicenter study with drotrecogin alpha has recently been initiated, to replicate the PROWESS study. Given the evidence that statin therapy reduces the rate of sepsis and sepsis-related mortality, studies with statins are underway [37–39]. Selenium, given as a high-dose supplementation, showed a beneficial effect in a subgroup of septic patients. Additional data on its beneficial effect in terms of outcome have stimulated new trials with pharmaconutrients [40,41]. The question is whether any positive effect can be expected in view of the design of the studies and the number of patients required to demonstrate a beneficial effect. Sepsis trials are nowadays designed in the same way as studies for myocardial infarction or cancer. However, dose-finding studies are scarcely performed, control or stratification for (infection) source control is omitted, and highly different ICUs with different mortality rates for their standard care can participate. The efficacy of the experimental treatment increases with the number of patients included [42]. These issues should be considered when future trials are designed.

**CONCLUSIONS**

Sepsis and severe sepsis are important in terms of morbidity and mortality. Increasing knowledge of the pathophysiology and results of recent trials are incentives for further studies of the pharmacological treatment of sepsis. Although not supported by large RCTs, the tuned use of vasoactive drugs to attain specific short-term goals contributes to the survival of severe sepsis patients. The complicated pattern of sepsis and the many interfering factors in patients with severe sepsis, demand in our view a more sophisticated design of future large-scale studies. Source control and level of ICU should be eliminated as confounders. Otherwise, a new wave

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**Table II** Putative future therapies in severe sepsis (Data from ClinicalTrials.Gov).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Clinical phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eritoran (ES564)</td>
<td>Toll-like receptor (TLR 4 Lipid antagonist</td>
<td>Phase II</td>
</tr>
<tr>
<td>TAK-242</td>
<td>Cytokine</td>
<td>Phase III</td>
</tr>
<tr>
<td>Recombinant platelet-activating factor acetylhydrolase (rPAF-AH, Pafase®)</td>
<td>Activated clotting cascade, platelet activation</td>
<td>Phase III</td>
</tr>
<tr>
<td>CytoFab (AZD9773)</td>
<td>Tumor necrosis factor (anti-TNF antibody)</td>
<td>Phase II</td>
</tr>
<tr>
<td>ART-123 (recombinant human soluble thrombomodulin)</td>
<td>Activated clotting cascade</td>
<td>Phase II</td>
</tr>
<tr>
<td>Granulocyte–macrophage-colony stimulating factor (GM-CSF)</td>
<td>Granulocyte/macrophage</td>
<td>Phase II</td>
</tr>
<tr>
<td>Atryn (anithrombin-alfa)</td>
<td>Activated clotting cascade</td>
<td>Phase II</td>
</tr>
<tr>
<td>GR270773</td>
<td>Binds to endotoxin</td>
<td>Phase I and II</td>
</tr>
<tr>
<td>Statins (simvastatin, atorvastatin, rosuvastatin)</td>
<td>HMG CoA-reductase (inhibition), immune modulation, unknown</td>
<td>Phase I, II and IV</td>
</tr>
</tbody>
</table>

of expensive, laborious studies which will again fail to demonstrate any effect on survival in patients with severe sepsis and septic shock may result.

REFERENCES
29 Annane D., Sebille V., Charpentier C. et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on


