Non-antibiotic strategies for sepsis

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Abstract

Sepsis and septic shock remain a considerable therapeutic challenge. Despite significant advances in supportive care and the availability of potent, broad-spectrum antibiotics, the overall mortality due to sepsis is still approximately 35%, and this increases to 60% if patients develop septic shock. Antibiotics constitute a necessary part of the treatment of sepsis, and there is probably considerable scope to improve the way in which they are used. Nevertheless, antibiotics alone, even used optimally, are probably not sufficient to substantially reduce the mortality that accompanies the multiorgan failure that occurs in septic patients. For this reason, considerable efforts have been expended in developing non-antibiotic (or so-called adjunctive) forms of treatment, and here the general approaches to these types of treatment are reviewed. There are three main categories: improvements in supportive care, treatments aimed at bacterial virulence factors, and treatments aimed at host mediators. This is not intended to be a comprehensive review, but rather to provide examples in each category to illustrate the general principles—and the hurdles—that have characterized these approaches to therapy.

Keywords: Antibiotic, cytokines, endotoxins, exotoxins, review, sepsis, shock, therapy, toll-like receptors


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Introduction

Large epidemiological studies and clinical trials in patients with sepsis have shown that the overall mortality rate is approximately 35% and that, in patients with more advanced disease, septic shock, the mortality rate increases to 60% or more. It is worth emphasizing that these alarming figures represent the outcome of ‘standard of care’ treatment; in other words, at least one-third of patients with this condition die, despite treatment on an intensive-care unit (ICU), receiving full supportive care and appropriate antibiotics. Sepsis is not rare [1,2]; it is one of the commonest causes of death on most ICUs. Why is it that this condition remains so challenging, despite all our efforts to improve the outcome? More particularly, why is it that antibiotics have not provided the answer? After all, sepsis is ‘simply’ the systemic response to infection, generally due to common bacterial organisms such as Staphylococcus aureus, streptococci, Enterobacteriaceae and Pseudomonas aeruginosa. Although we rarely know the exact microbiological diagnosis when the patient first presents, we now have at our disposal a wide array of broad-spectrum antibiotics that can—and should—be deployed empirically. Why is it that this has seemingly not been sufficient to make a significant impact on the progress of the disease?

There are, perhaps, two answers to this question. We should first acknowledge that antibiotics are indeed highly effective, but that we need to use them appropriately. Sepsis is most effectively managed when it is recognized early and treatment is started quickly. This is well illustrated by a recent study that demonstrated a clear relationship between the delay in starting antibiotics and the eventual outcome [3]. When antibiotics were started within 1 h of documented hypotension, survival was 79.9%. Each subsequent hour of delay over the next 6 h was associated with an average decrease in survival of 7.6%. Furthermore, the antibiotics chosen need to be appropriate. Several clinical trials demonstrated that there was a significant difference in the outcome when the regimen used empirically was subsequently shown to be active against the causative organism [4,5]. This is a matter not just of spectrum of activity, but also of pharmacodynamics, an aspect of the antibiotic treatment of septic patients that has perhaps been under-appreciated [6–8].

But the second explanation for the failure of conventional therapy is that the pathophysiology of sepsis is the result of a highly complex set of processes in which the host response becomes deregulated and causes cellular damage, tissue damage, and, ultimately, organ damage. Although antibiotics are necessary elements in the treatment of sepsis by the time that the clinical picture has been recognized they are
unlikely to be sufficient alone, and it is for this reason that so much attention has been paid to adjunctive therapies that might address the underlying pathological processes. This is the focus of this special theme section of the journal.

It is not the purpose of this overview to present a complete and detailed review of every aspect of the subject, but rather to provide a framework in which to consider the other articles in this section. There are three broad approaches to adjunctive (non-antibiotic) therapy that need to be considered (Table 1).

### Improving Supportive Care

In developed countries, most septic patients are cared for in the ICU, and the treatment of septic patients represents a collaboration between intensive-care and infection specialists. There have been substantial developments in the haemodynamic management of sepsis, which, although not of specific interest to infection practitioners, have contributed substantially to reducing the morbidity and mortality of the disease. A detailed analysis of these trials is not relevant here, but, as an example of a non-antibiotic strategy that recently attracted much attention, I will briefly discuss the concept of early goal-directed therapy.

During the 1980s, several investigators, notably William Shoemaker, suggested that clinical outcomes in sepsis might be improved by manipulating haemodynamic variables to some predefined targets that would optimize oxygen delivery and utilization by the tissues. Attaining a cardiac index >4.5 L/min/m², an oxygen delivery index >600 mL/min/m², and oxygen consumption >170 mL/min/m² became the ‘goals’, and the strategy was ‘goal-directed therapy’. Unfortunately, the subsequent clinical trial evidence did not show that this ‘one size fits all’ approach was effective, and it fell into disuse. It was against this background that, in 2001, Rivers published a startling paper in which he described the effects of early goal-directed therapy, a more customized approach used for the first 6 h after patients presented in the emergency room with sepsis [9]. In a prospective, randomized controlled trial of 263 patients, the in-hospital mortality was 30.5% in the treatment group vs. 46.5% in the controls, a remarkable 16% drop in relative mortality and a highly significant result (p 0.009). This was achieved with a relatively straightforward protocol, in which central venous pressure, mean arterial pressure and central venous oxygen saturation (ScvO₂) were monitored and manipulated with fluids or vasoactive drugs to achieve predefined endpoints.

Subsequently, the generalizability of this approach has been challenged, and a further clinical trial is currently underway to determine whether the findings can be confirmed. Nevertheless, it is a good illustration of how detailed attention to fluid management, vasoressor use and optimization of oxygen delivery are critical to the ‘non-antibiotic’ management of sepsis. A comprehensive consensus statement that summarizes the evidence for various aspects of supportive care has recently been published [10].

### Bacterial Targets

It would seem axiomatic that bacterial virulence factors should be highly attractive therapeutic targets, as presumably they initiate the pathological effects of the infection, even if in sepsis it is host mechanisms that perpetuate and amplify those effects.

An important concept to emerge in recent years has been that of pathogen-associated molecular patterns (PAMPs) and their role in engaging the host innate immune response in what I have termed the molecular architecture of sepsis [11] (Fig. 1). At its core, the host–pathogen interaction needs a mechanism by which the elements of the host innate immune system can recognize, and respond to, the presence of bacteria. PAMPs constitute one side of this interaction; pathogen recognition receptors (see below) constitute the other.

Many PAMPs have been identified and their structure has been described in great detail (some examples are shown in Table 2); several of them have been intensively investigated as potential therapeutic targets. Two examples will serve to demonstrate both the principles and the frustrations of this approach.

### Gram-negative endotoxin

A very substantial body of evidence has implicated endotoxin (lipopolysaccharide (LPS)) of Gram-negative bacteria as a major cause of the myriad of physiological changes seen in the septic patient (reviewed in [12,13]), and LPS was probably the very first target for the development of a non-antibiotic treatment for sepsis. Injecting animals with LPS can

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**TABLE 1. General approaches to the adjunctive treatment of sepsis**

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Example</th>
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<tbody>
<tr>
<td>Improve supportive care</td>
<td>Oxygenation/ventilation strategies; optimize fluid/vasopressor use; early goal-directed therapy</td>
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<tr>
<td>Target bacterial virulence factors</td>
<td>Anti-endotoxin antibodies, endotoxin-removal columns</td>
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<tr>
<td>Target host response factors</td>
<td>Corticosteroids; anticytokine drugs; anticoagulants</td>
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reproduce most of the pathological features of sepsis, and experimental approaches that remove or neutralize LPS can successfully modify the disease; animals that are genetically resistant to LPS are essentially protected from the lethal effects of LPS. Furthermore, LPS can be found in the circulation of many (but not all) patients with septic shock, including, interestingly, some with Gram-positive infections. Yet in the main, the clinical development of anti-endotoxin strategies has been unsuccessful. The single (possible) exception is a Japanese product that acts as an extracorporeal LPS-removal device; this is commercially available in Japan, but controlled trial data from Europe have not provided clear evidence of benefit [14]. There are a number of possible reasons for this failure, including the probably transitory nature of endotoxin in the circulation, and problems in generating an effective neutralizing antibody to the lipid-containing ‘toxic core’ of LPS.

Exotoxins from Gram-positive bacteria
The second example of PAMPs comes from Gram-positive bacteria. Exotoxins from staphylococci and streptococci should theoretically be much easier targets. Exotoxins such as toxic shock syndrome-1 from *S. aureus* and the pyrogenic exotoxins of *Streptococcus pyogenes* are proteins (and therefore much more amenable to antibody neutralization), and are clearly implicated in the pathogenesis of conditions such as staphylococcal or streptococcal toxic shock syndromes (reviewed in [15,16]). Here again, though, the clinical development of therapeutic agents has been frustrated, in this case because there are no good assays with which to demonstrate the presence of the toxins in the circulation, and because these conditions are relatively uncommon; by the time they have been clinically identified, it is probably too late to be able to intervene usefully with antitoxin drugs or antibodies.

Targeting bacterial PAMPs remains a theoretically very attractive approach, and will continue to attract considerable interest, but for the moment there are significant practical problems to be overcome.

**Host Targets**

As we have seen, although bacteria (through their PAMPs) initiate the septic response, it is the dysregulated host immune response that amplifies the process and causes the cellular injury that ultimately leads to the characteristic picture of multiorgan failure. There have been phenomenal advances in understanding the intricacies of the host response to sepsis which have been well reviewed elsewhere [17], and these have provided a rich source of potential targets [18] (Table 3). Broadly, two different approaches have been pursued: what might be called ‘immunosuppression’,

**TABLE 2.** Examples of bacterial virulence determinants (pathogen-associated molecular patterns) associated with initiation of the septic response

<table>
<thead>
<tr>
<th>Gram-negative bacteria</th>
<th>Endotoxin (lipopolysaccharide)</th>
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<tr>
<td></td>
<td>Peptidoglycan</td>
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<td></td>
<td>Flagellin</td>
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<td>Porens</td>
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<td>CpG DNA</td>
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<td></td>
<td>Triacyl lipopeptides</td>
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<tr>
<td>Gram-positive bacteria</td>
<td>Peptidoglycan</td>
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<tr>
<td></td>
<td>Lipoteichoic acid</td>
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<td></td>
<td>Exotoxins</td>
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The first major clinical trials of steroids in the treatment of sepsis date back to the 1980s. A substantial body of preclinical data had suggested that many of the manifestations of sepsis were due to excess inflammation, and that anti-inflammatory doses of steroids would be beneficial. Indeed, in various animal models, including primates, steroids were very effective. On the basis of these findings, two large clinical trials of high-dose steroids were conducted and both concluded that these high-dose regimens were not effective in preventing death from sepsis, or, indeed, were perhaps even harmful, increasing the risk of superinfection [19,20].

More recently, Annane et al. suggested that some septic patients failed to respond adequately to the physiological ‘stress’ that occurs in sepsis. On the basis of pilot data showing that small doses of hydrocortisone reduced vasoressor dependency, they proceeded to carry out a prospective, randomized controlled trial in which patients with septic shock received replacement doses of hydrocortisone plus fludrocortisone or matching placebos, for 7 days [21]. They enrolled 300 patients, and the main outcome measure was 28-day survival in patients who were shown to have adrenocortical insufficiency on the basis of a corticotropin test. There were fewer deaths in the active treatment group: 73 vs. 60, p 0.02.

It is still not clear whether this approach is genuinely based on ‘replacement therapy’ or is, in fact, simply a more modest dose of immunosuppression, and, indeed, the recent CORTICUS trial, which attempted to repeat the findings of the original study, failed to reproduce the beneficial outcome [22]. A recently updated meta-analysis has tentatively concluded that low-dose steroids are beneficial for the subset of patients at high risk of death [23] but, in the absence of a trial that specifically addresses this question, the debate is likely to continue for some time.

The use of IVIG in sepsis also has a long history [24]. It was initially thought that it might be useful because it contained anti-endotoxin antibodies [25] but, despite several clinical trials, this idea never really gained currency, and IVIG has largely disappeared from routine clinical use for sepsis with the exception of patients with streptococcal toxic shock syndrome (STSS). Group A streptococci produce exotoxins that have the property of superantigens, and it is this that is thought to underlie many of the manifestations of STSS (reviewed in [15]). Commercial preparations of IVIG contain antibodies to one of the major streptococcal exotoxins, streptococcal pyrogenic exotoxin A, [26], and it was thought that this might explain the somewhat anecdotal clinical evidence that large doses of IVIG seemed to be beneficial in this disease [27,28]. However, it has subsequently emerged that streptococcal pyrogenic exotoxin A is just one of many superantigenic toxins produced by streptococci, and it is not even the most potent.

If IVIG is indeed effective—and the clinical trial data are not of level 1 quality, either for STSS or, more generally, for sepsis [29]—then it is more likely that it is acting as a non-specific immunosuppressant, in much the same way as it is effective in idiopathic thrombocytopenic purpura. In a very real sense, treating severe infection with immunosuppressives is counterintuitive, and the risk of making things worse and/or causing secondary infections is one of the main concerns with this approach. A more attractive strategy is targeted immunotherapy.

Cytokines. Tumour necrosis factor (TNF) is probably the best known example of a specific cytokine mediator that has been extensively investigated as a therapeutic target for sepsis (reviewed in [30]). Various strategies were pursued, including both polyclonal and monoclonal antibodies, antibody fragments, and receptor constructs. However, despite a substantial body of encouraging preclinical evidence and several large phase III clinical trials, no anti-TNF strategy has succeeded. Subsequently, other anticytokines were also investigated, including interleukin-1 receptor antagonist and interleukin-6 antibody, with similar outcomes. The reasons for these failures have been much debated [31]. A commonly held view is that redundancy of the cytokine network means that neutralizing or blocking a single pathway will fail to interrupt the overall process; thus, even if we successfully neutralize TNF, for instance, the inflammatory process will simply ‘bypass’ the blockade and continue unabated. This may be partly true, although it does not explain why blocking

<table>
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<th>TABLE 3. Some examples of components of the host immune response to sepsis that have been considered as potential therapeutic targets</th>
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<td>Toll-like receptors</td>
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<tr>
<td>Complement proteins</td>
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<td>Cytokines</td>
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<td>Nitric oxide synthase</td>
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<td>Coagulation proteins</td>
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<td>Lactoferrin</td>
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<td>HMG box-1 protein</td>
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<td>Adenosine A2A receptors</td>
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<td>A7 nicotinic acetylcholine receptors</td>
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For a full discussion, see [18].
cytokines in animal models is so successful. It is certainly true that both TNF and interleukin-1 are ‘early-response’ cytokines, and that attempts to block them in clinical practice may simply be too late. However, another view is that the studies failed not because the underlying science was ‘wrong’, but because of the challenges in carrying out clinical trials in a very complex patient population [32]. What is certainly true is that most of the clinical trials of the anticytokine reagents were hampered by the fact that there was no good way of showing that patients actually had a derangement of the target molecule (e.g. a raised TNF serum level) at the time that the drug (e.g. anti-TNF) was administered. This meant that many patients were entered into the trials who were probably unlikely to benefit, increasing the ‘signal-to-noise’ ratio and making it harder to achieve a statistically significant result.

Coagulation cascade. It had been known for some time that the coagulation cascade was just one of several pathways that were deranged in septic patients. Drotrecogin alfa (activated) (activated protein C) was developed on the basis of the observation that protein C, a naturally occurring anticoagulant protein, was consumed in sepsis and that the extent of the consumption correlated with the outcome. Preclinical studies showed that replacement with activated protein C prevented death in animal models of sepsis. The landmark study by Bernard et al. [33] showing a survival benefit with drotrecogin alfa (activated), led to registration by both the European Medicines Agency and the US Food and Drug Administration, and approval from the National Institute for Health and Clinical Excellence for its use in defined clinical settings. Nevertheless, the lack of a second confirmatory clinical trial and the failure of the ADDRESS study in lowerrisk patients [34] means that many intensive-care specialists remain uncertain about the precise role of this drug. Indeed, a very recent Cochrane review concluded that “Unless additional RCTs provide evidence of a treatment effect, policymakers, clinicians and academics should not promote the use of (activated protein C)” [35]. Notwithstanding the ongoing debate about the efficacy of the drug [36] (and its mode of action), drotrecogin alfa (activated) provides an interesting example of the next level of sophistication of the drug development programme, because protein C can be measured in septic patients, and, indeed, a trial currently in progress is measuring serum levels in real time and modifying therapy accordingly.

Toll-like receptors. I noted above that the host–pathogen interaction has two components: the first comprises bacterial PAMPs; these are then recognized by the second element, pathogen recognition receptors on host cells. Toll-like receptors (TLRs) are a family of receptors that sense PAMPs and initiate a signal that is handed through a cascade of molecules, leading to activation of nuclear factor-κB and, ultimately, mRNA transcription of cytokines (for reviews see [37–39]). TLR4 turned out to be the long-sought receptor for endotoxin, and quickly became a potential drug target [40,41]. Preclinical studies have already been completed, and clinical trials are underway. It remains to be seen whether blocking endotoxin sensing at the level of TLR4 will be effective. One concern is that by the time the clinical manifestations of endotoxaemia are apparent, blocking the receptor may be too late—locking the stable door after the horse has bolted.

Conclusions

Reducing the mortality due to sepsis and septic shock is a key medical need that remains unmet, but designing the appropriate vehicle with which to evaluate new agents has been particularly challenging. More than 10 years ago, investigators began to think about some of the practical difficulties (see, for instance, a series of reviews in [42]), and many of the concerns about sample size, use of appropriate definitions, and statistical methodology have been revisited more recently [43,44]. Such has been the concern that we have suggested that a better approach would be to abandon the attempt to design trials in ‘sepsis’ as such, but instead to focus on specific infectious disease syndromes associated with markers of severity [32]. It is salutary to note that, more than 10 years after we reviewed the field of adjunctive therapy for sepsis [45], there is still only one licensed drug available despite several thousand patients having been entered in large international clinical trials. The articles included in this current special theme section of the journal describe the ongoing efforts to establish new treatment modalities for what remains a highly challenging disease.

Transparency Declaration

The author declares that no conflict of interest exists.

References


