Adjunctive therapy in sepsis: a critical analysis of the clinical trial programme

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*He that will not apply new remedies must expect new evils; for time is the greatest innovator.*

On innovations

*Essays*, Francis Bacon, 1561–1626

Despite intensive efforts, the development of novel drugs for the treatment of sepsis has proved to be extremely difficult. A large number of clinical trials have ended in failure. A critical analysis of this record suggests that there is no single reason for these problems. Rather, the explanation lies in part with unexpected failures in the drugs themselves, and in part with the difficulties of trial design in this particular group of patients. In future, trials in this area are likely to be more highly focused, with even stricter protocol definitions to try and ensure a homogeneous patient population.

The concept of immunotherapy has had a very distinguished history. Active immunisation began on 14 May, 1796 when Edward Jenner, a young rural medical practitioner inoculated an 8 year-old boy with fluid taken from the cowpox vesicles on the hand of a milk-maid. When, in the following July, the boy was exposed to smallpox he remained well and no disease developed. Later, Robert Koch was the first to use passive immunisation when he gave a young German girl who was dying of diphtheria an injection of sheep serum containing neutralising antibody to the diphtheria toxin. Remarkably, the girl survived and made a full recovery.

Although the principle of active immunisation went on to provide the basis of prevention of many important infectious diseases, treatment of acute episodes depended on passive immunotherapy. As late as 1935, Maxwell Finland, in the Boston City Hospital in the US, was using equine serum to treat pneumococcal pneumonia and it was only the introduction of penicillin during the Second World War that led to the rapid decline in interest in passive immunotherapy for the treatment of infections.
The notion that passive immunotherapy might be used in sepsis can really be traced back to the early 1970s and the work of Chedid, Braude and McCabe (for a review of the early experimental work see Appelmelk & Cohen). These studies focused on the generation of antibodies to the core structures of endotoxin and, for a long time, this was what was understood by 'immunotherapy in sepsis'. During the 1980s, there was an explosion of knowledge concerning the basic immunological mechanisms involved in the pathogenesis of sepsis and, at the same time, technical advances made it possible to develop monoclonal antibodies for possible therapeutic use. These changes opened up extraordinary possibilities, and 'immunotherapy' came to encompass the wide range of immunologically-based strategies having as a target microbial components (such as endotoxin, or host factors such as cytokines and their receptors, mediators such as complement, or arachidonic acid pathway components), or cellular targets such as adhesion molecules. More recently, much effort has gone into the development of pharmacological (rather than immunological) strategies: examples are platelet activating factor antagonists, or inhibitors of bradykinin. In fact, many of the problems are the same, and rather than talk about immunotherapy, a better term is probably adjunctive therapy since this captures all types of agents.

The current situation

A huge number of drugs and immunological agents have been studied as potential adjunctive therapy for sepsis (reviewed by Lynn & Cohen). Inevitably, most of them have not progressed beyond in vitro testing or early preclinical evaluation but, in some cases, extensive clinical experience has been gained. Table 1 summarises the outcome of the major clinical trials in this area, at the time of writing (June 1998).

Anti-endotoxin strategies

There is overwhelming evidence that endotoxin is the 'toxic principle' of Gram-negative bacteria (reviewed by Morrison). Biochemically, endotoxin is a lipopolysaccharide having an inner lipid component (lipid A), a core region and the outer O polysaccharide chain. Recognition that most of the 'toxic' properties of endotoxin resided within the inner structures suggested that neutralising antibodies directed against the core glycolipid or the lipid A might be potent 'anti-endotoxins'. Since the structure of endotoxin was largely conserved, irrespective of the bacterial species from which it was derived, it seemed possible that such antibodies might be extremely valuable therapies since it would not be
<table>
<thead>
<tr>
<th>Target</th>
<th>First author (citation)</th>
<th>Intervention</th>
<th>Study design (No. of patients)</th>
<th>Principal findings</th>
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<tr>
<td><strong>Anti-endotoxin strategies</strong></td>
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<tr>
<td>1 Endotoxin E. coli J5</td>
<td>Ziegler</td>
<td>Polyclonal human antiserum</td>
<td>RPCT (212)</td>
<td>Reduced mortality in GN bacteraemia</td>
</tr>
<tr>
<td>2 Endotoxin E. coli J5</td>
<td>Baumgartner*</td>
<td>Polyclonal human antiserum</td>
<td>RPCT of prophylaxis (262)</td>
<td>Reduced morbidity and mortality following GN infection in surgical patients</td>
</tr>
<tr>
<td>3 Endotoxin S. minnesota RS95</td>
<td>IVIG Collaborative study group*</td>
<td>High – titre IVIG</td>
<td>RPCT (352)</td>
<td>No benefit</td>
</tr>
<tr>
<td>4 Endotoxin lipid A</td>
<td>Ziegler*, Centoxin</td>
<td>HA-1A human monoclonal anti-lipid A</td>
<td>RPCT (543)</td>
<td>No overall benefit improvement in GN bacteraemia</td>
</tr>
<tr>
<td>5 Endotoxin lipid A</td>
<td>McCloskey*, CHESS</td>
<td>HA-1A human monoclonal anti-lipid A</td>
<td>RPCT (2199)</td>
<td>No benefit</td>
</tr>
<tr>
<td>6 Endotoxin lipid A</td>
<td>French HA-1A*</td>
<td>HA-1A human monoclonal anti-lipid A</td>
<td>RPCT (600)</td>
<td>No benefit</td>
</tr>
<tr>
<td>7 Meningococcal LPS</td>
<td>Unpublished</td>
<td>HA-1A human monoclonal anti-lipid A</td>
<td>RPCT in children (270)</td>
<td>Details not yet published; 30% reduction in mortality; not statistically significant</td>
</tr>
<tr>
<td>8 Endotoxin lipid A</td>
<td>Greenman*</td>
<td>E5 murine monoclonal anti-lipid A</td>
<td>RPCT (468)</td>
<td>No overall benefit; possible improvement in GN infections without shock</td>
</tr>
<tr>
<td>9 Endotoxin lipid A</td>
<td>Bone*</td>
<td>E5 murine monoclonal anti-lipid A</td>
<td>RPCT (830)</td>
<td>No overall benefit; trend to improvement in organ function in shock</td>
</tr>
<tr>
<td>10 Endotoxin lipid A</td>
<td>Unpublished</td>
<td>E5 murine monoclonal anti-lipid A</td>
<td>NK</td>
<td>Details not yet published but E5 now withdrawn from development</td>
</tr>
<tr>
<td>11 Endotoxin entero- bacterial common antigen</td>
<td>Panacek*</td>
<td>T88 human monoclonal antibody</td>
<td>RPCT (826)</td>
<td>No benefit</td>
</tr>
</tbody>
</table>

| **Anti-TNF strategies** | | | | |
| 12 TNF | Abraham*, NORASEPT | Murine monoclonal anti-TNFab | RPCT (994) | No overall benefit; patients in shock benefited during first 72 h |
| 13 TNF | Cohen*, INTERSEPT | Murine monoclonal anti-TNFab | RPCT (564) | No overall benefit; improved shock reversal and reduced frequency of organ failures |
| 14 TNF | Abraham*, NORASEPT II | Murine monoclonal anti-TNFab | RPCT (1878) | No benefit |
| 15 TNF | Reinhart*, MAK 195F study | Anti-TNF, F(ab)′2 | RPCT (122) | No overall benefit; retrospective analysis suggested benefit in patients with elevated IL-6 |
| 16 TNF | Unpublished | Anti-TNF F(ab)′2 | RPCT in patients with IL-6 > 1000 ng/ml | Details not yet published; study discontinued for futility |
| 17 TNF | Fisher* | p75sTNFR | RPCT (141) | Dose-dependent increased mortality in active group |
| 18 TNF | Abraham* | p55sTNFR | Phase II RPCT (498) | 33% reduction in mortality patients with severe sepsis |
| 19 TNF | Unpublished | p55sTNFR | Phase III RPCT (1342) | Details not yet published, study failed to show efficacy |
Table 1 (continued) A summary of the major clinical trials of adjunctive agents for the treatment of sepsis

<table>
<thead>
<tr>
<th>Target</th>
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<th>Study design (No. of patients)</th>
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<tbody>
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<td><strong>Other anti-cytokine strategies</strong></td>
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<tr>
<td>20 IL-1</td>
<td>Fisher17</td>
<td>IL-Ira</td>
<td>RPCT (893)</td>
<td>No overall benefit; possible improvement in patients with predicted mortality &gt; 24%</td>
</tr>
<tr>
<td>21 IL-1</td>
<td>Opal28</td>
<td>IL-1ra</td>
<td>RPCT (696)</td>
<td>Study terminated for futility at interim analysis</td>
</tr>
<tr>
<td><strong>Other pharmacological strategies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22 PAF</td>
<td>Dhainaut29</td>
<td>BN 52021</td>
<td>RPCT (262)</td>
<td>No overall benefit; retrospective analysis suggested benefit in patients with GN bacteraemia</td>
</tr>
<tr>
<td>23 PAF</td>
<td>Gourlay40</td>
<td>BN 52021</td>
<td>RPCT in GN sepsis (608)</td>
<td>No benefit</td>
</tr>
<tr>
<td>24 Cyclo-oxygenase pathway</td>
<td>Bernard41</td>
<td>Ibuprofen</td>
<td>RPCT (455)</td>
<td>No benefit on ARDS or mortality</td>
</tr>
<tr>
<td>25 Thromboxane</td>
<td>Yu42</td>
<td>Ketoconazole</td>
<td>RPCT of prophylaxis (54)</td>
<td>Significant reduction in development of ARDS and mortality</td>
</tr>
<tr>
<td>26 Clotting cascade</td>
<td>Fourrier43</td>
<td>Replacement of AT III</td>
<td>RPCT (35)</td>
<td>44% reduction in mortality not statistically significant; duration of DIC significantly reduced</td>
</tr>
<tr>
<td>27 Bradykinin</td>
<td>Fein44</td>
<td>BK antagonist deltibant</td>
<td>RPCT (504)</td>
<td>No benefit</td>
</tr>
<tr>
<td>28 Nitric oxide</td>
<td>Unpublished</td>
<td>L-NMMA</td>
<td>RPCT</td>
<td>Details not yet published, study terminated for safety concerns</td>
</tr>
<tr>
<td>29 Toxic oxygen species</td>
<td>Spies45</td>
<td>N-acetyl cysteine</td>
<td>RPCT (58)</td>
<td>Transient benefit in tissue oxygenation; no effect on survival</td>
</tr>
</tbody>
</table>

RPCT = randomised placebo controlled trial; GN = Gram-negative; TNFR = TNF receptor; NK = not known.
necessary to wait for microbiological confirmation of the diagnosis: any patient with clinically suspected Gram-negative sepsis could be given the antibody with the reasonable expectation that the circulating endotoxin would be neutralised. The first two phase III trials to be done used a polyclonal antiserum raised against *Escherichia coli* JS, a strain of *E. coli* which had lost most of its O side chain and with core glycolipid exposed on the bacterial cell surface. These two studies\(^5,6\) both seemed to show benefit but crucially, in neither case could it be proven that the positive outcome was specifically due to an increase in the titre of the putative 'protective' antibody. The subsequent work in this area focused mainly on two monoclonal antibodies directed against lipid A. HA-1A was a human antibody; the first trial reported a benefit in a subset of patients with Gram-negative bacteraemia\(^7\) and, on the strength of this, the drug was briefly licensed in some countries. However, the study design was heavily criticised and, when a second trial was conducted, the positive findings were not confirmed\(^8\). It has subsequently emerged that HA-1A was probably binding non-specifically to Gram-negative bacteria\(^9\). The second anti-lipid A was a mouse monoclonal antibody; it took three large phase III trials to show that this too had no consistent effect on survival (Table 1). The antibody approach to endotoxin is no longer being pursued, but endotoxin is still an attractive target. Other anti-endotoxin strategies being studied include LPS binding drugs such as bactericidal/permeability-increasing protein (BPI)\(^10\) and lipoproteins\(^11\).

**Anti-TNF strategies**

There can hardly be a better example of the frustrations and difficulties associated with this field than the story of attempts to neutralise TNF in sepsis. The preclinical data were very clear and provided a sound basis for large scale clinical trials. The first approach was a murine monoclonal antibody, BAY x1351. In two separate trials, there was an indication that the antibody was active but the effect was modest at best (Table 1). When a third study was done in almost 2000 patients, absolutely no benefit was seen. A slightly different approach was used by Reinhart et al, who used an F(ab')\(_2\) fragment of an antibody called MAK195F\(^12\). In a rather small study, a retrospective analysis suggested that it might be active in patients who had an interleukin-6 (IL-6) level of >1000 ng/ml at study entry. This seemed plausible, since it was known that IL-6 was a marker of severity. A follow-up trial was carried out to test this hypothesis prospectively, but the study was terminated when it failed a futility analysis. A second study with this drug is still in progress in the US; it is enrolling all patients, irrespective of IL-6 levels, but IL-6 levels are being recorded and efficacy will be compared in the high and low-level groups.
Another way to neutralise TNF is by making constructs of the soluble TNF receptor with the Fc piece of immunoglobulin. These can use either the p55 type I receptor or the p75 type II receptor. Both are very effective at neutralising TNF, probably more so than the anti-TNF antibodies. The first trial was done with the p75 construct but, surprisingly, this showed a significant increase in mortality with the higher dose group. The reason is not absolutely clear, but may have been related to the instability of the receptor complex with TNF. This did not seem to be a problem with the p55 complex, and a large phase II study with this drug in sepsis showed benefit. Once again though, a follow-up phase III trial concluded that the drug was ineffective.

Other strategies

Interleukin-1 receptor antagonist (Il-1ra) is a naturally occurring cytokine which competes with IL-1 for occupancy of the IL-1 receptor but, when it occupies the receptor, it does not activate the cell. Preclinical studies showed that blocking IL-1 was a very effective therapy for sepsis, but when IL-1ra was tried clinically it failed. Other pharmacological strategies that have been subjected to phase III studies in sepsis are listed in Table 1. The story is the same: despite convincing preclinical data, none of the drugs showed clinical benefit.

More than 15,000 patients have now been entered into approximately 25 phase III trials in sepsis, but to date no intervention has shown unequivocal evidence of benefit. Where have we gone wrong?

Explanations

The targets are wrong

The evidence that endotoxin, the pro-inflammatory cytokines, and the other mediators that have been identified as therapeutic targets play a pivotal role in the pathogenesis of sepsis is extremely strong. The preclinical data point very clearly to the fact that, at least in experimental animal models, blocking or neutralising these mediators will prevent death from sepsis. Of course, the failure of the clinical trials means that, ipso facto, we cannot formally conclude that endotoxin or TNF play the same pivotal role in human disease. However, the fact that neutralising TNF in rheumatoid arthritis, for instance, is clearly beneficial suggests that TNF is indeed an important biological molecule in man. It may also be true that the regulatory mechanisms are more complex in the clinical setting than in mice, or that humans respond
differently. Indeed, a good example of this is the differing sensitivity of various species to endotoxin: rodents are highly resistant and can tolerate doses several orders of magnitude greater than humans. Despite these caveats, there is wide agreement that in the correct setting the targets that have been studied are appropriate.

The drugs are wrong

The clinical trials may have failed because the drugs were ‘wrong’ in a number of different ways. First, they may have been ineffective because they simply did not do what was intended. The best example of this is HA-1A, a monoclonal antibody which was meant to bind to and neutralise the lipid A of endotoxin. Although initial studies did seem to show this specificity, it was shown later that the binding was non-specific, and this is the most likely explanation for the failure of those studies. Another possibility is that although active in vitro against the desired target, the drug was simply not sufficiently potent in vivo. This is possibly part of the explanation for the failure of the anti-TNF monoclonal antibody Bay x1351, which was only moderately active in comparison with the TNF receptor constructs, and did not show convincing reductions of TNF levels in septic patients.

Pharmacological and/or pharmacokinetic considerations are also potentially important. Issues such as half-life, tissue penetration and dose regimens all have a powerful influence on the efficacy of a drug. For instance, although cytokine levels are usually measured in the serum, it may be that tissue levels are more relevant. IL-1ra may have failed in part because of the very large doses that seemed to be needed to displace native IL-1 from its receptor.

Finally, the drugs may have been ‘wrong’ in that they caused unexpected toxicity. Several of the clinical trials failed for this reason. The p75 type II TNF receptor construct caused a dose-dependent significantly higher mortality in the treatment arm, despite encouraging initial trial data. The reasons are not entirely clear: one possibility was that the drug was less active against Gram-positive infections, another that it was caused by the instability of the TNF-receptor binding. Another failure in this category was L-NMMA, a competitive inhibitor of inducible nitric oxide synthase. Here, the preclinical data were more equivocal since some of the animal model studies had also shown an increased mortality. However, a phase II study had suggested that the drug was effective so a large phase III trial began. Unfortunately, ongoing safety analyses showed a significantly higher mortality in the treatment group and the study was stopped prematurely. Clearly then a number of the failures of the clinical trial programme are relatively easy to attribute to failures of the drug, for one
reason or another. However, not all the trials fall into this category, and we must look for other explanations.

**Trial design**

**Definitions of sepsis**

The starting point for all clinical trials is the entry of patients who fulfil certain prespecified criteria. This has proven to be a particularly difficult and controversial area in regard to sepsis. Paradoxically, ‘septicaemia’ is a condition which most doctors feel able to recognise at the bedside but which is extraordinarily difficult to define.

A key step was the proposal by Bone to adopt the terms sepsis, sepsis syndrome, and septic shock. The main element of the sepsis syndrome was that there should be evidence of a systemic response to infection (although the site of the infection may not be identified and it need not be microbiologically confirmed). Septic shock was essentially the same but with superadded haemodynamic instability. The so-called ‘Bone criteria’ were widely accepted and formed the basis of a large number of clinical trials but, over time and with greater experience, a number of problems emerged. The first, and potentially the most important, is the very heterogeneous nature of the population who fall within these supposedly rather well-defined criteria. This heterogeneity applies both to the underlying disease (in other words, the pre-existing pathology which led to them developing sepsis) and to the severity of the sepsis syndrome itself. For instance, in the population in which the concept was first tested (a clinical trial of methylprednisolone) the mortality varied between 13% and 43%, depending on the presence of shock. Conversely, in some respects the definition was found to be too prescriptive: common signs included in the sepsis syndrome such as fever, tachycardia or tachypnea are sometimes not seen even though the patient is by all other criteria ‘obviously’ septic.

One of the components of the sepsis syndrome that puzzled and sometimes frustrated investigators was the requirement for patients to be infected. They pointed out that it was not uncommon for patients with severe inflammation to exhibit all the features of sepsis yet not be infected – the example often quoted was that of acute pancreatitis. In response to this a new syndrome was proposed – the systemic inflammatory response syndrome, SIRS. The criteria which defined SIRS were very simple; two or more of the following conditions were required: (i) temperature > 38°C or < 36°C; (ii) heart rate > 90 bpm; (iii) respiratory rate > 20 breaths/min or PaCO₂ < 32 mmHg; or (iv) white blood cell count > 12000 mm⁻³, < 4000 mm⁻³, or > 10% band forms.

SIRS was a useful idea conceptually in that it emphasised the ‘final common pathways’ of infection and inflammation, but many feel that it
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has not been helpful clinically, largely because it was so sensitive that the majority of ICU patients fulfilled the criteria and SIRS did not usefully define a recognisable group of patients. One response to this was to add some form of 'severity score', or risk assessment adjustment, to the equation. The merits of this have been discussed extensively; the key issue is whether the method can be used prospectively, and that it is validated for the kind of patients in whom it is to be used. However, what is clear is that patients who fulfil the SIRS criteria (and even patients who fulfil the more rigorous definitions of 'proper' sepsis) embrace a wide range of severity – the mortality can vary as much as 70%. This too has been a major source of problems in trials; clearly, such a heterogeneous population is not ideal for testing a drug. Patients who are too ill are unlikely to benefit however good the drug, while patients at the other end of the scale simply produce statistical 'noise' and may dilute the potential benefit.

Although there has been a move back towards using definitions of sepsis which include infection as a sine qua non, the question of whether this is a valid clinical entity remains. Are we really sure that a young man with meningococcal sepsis, an elderly woman with a postoperative Klebsiella pneumonia and a young drug addict with Staphylococcus aureus endocarditis and a ruptured valve really have the same pathological process which is amenable to the same kind of therapeutic intervention? I rather doubt it.

Definitions of infection

Remarkable little attention has been paid to how infection should be recognised and defined in clinical trials of sepsis. The usual form of words found in trial protocols is 'clinical evidence of infection', often with little else by way of explanation. Even less is found concerning the microbiological methods to be used. This has been discussed in more detail elsewhere; suffice it to say here that it represents an important potential cause of variability in sepsis studies.

Protocol design issues

With such a complex patient population that requires many types of medical intervention, it is not surprising that many other factors have emerged which represent potentially important sources of variability, and thus error. One example of this is concomitant therapy, particularly with antibiotics. It was established many years ago that inappropriate antibiotic therapy was associated with a significantly worse outcome than the correct treatment. Hence, comparing the efficacy of a novel agent in patients who may not have received equally effective antimicrobial therapy is not a 'level playing field'. Attempting to address this by specifying the antimicrobial therapy in the protocol has been
thought to be impractical, both because of differences in the use and availability of antibiotics in different parts of the world, and because the ‘correct’ antimicrobial regimen will depend on the clinical circumstances and, hence, is difficult to prescribe. The only realistic approach is to include an independent assessment of the antimicrobial therapy for each patient in the post hoc analyses of comparability. The same considerations, of course, apply to all the other modalities of therapy even though it is sometimes less clear that they have such a direct effect on outcome. One area though that should certainly be considered is the adequacy of source control.

Timing

It is acknowledged that there is probably a ‘window’ of opportunity during which adjunctive agents are most likely to be effective. Treating too early, and in particular too late, is likely to be unhelpful and at worse, actually harmful. What is not agreed are the limits of this window. Indeed, it is unlikely to be the same for all clinical conditions of sepsis, yet another example of the ‘lumping philosophy’ which has bedevilled this area. Most clinical trial protocols have set some kind of limit to the period during which the entry criteria must be fulfilled. Interestingly, in the earlier trials, these limits were often rather generous (e.g. 12 h or more), presumably reflecting the wish to be as inclusive as possible and not make enrolling patients too difficult. The result of this was to enrol many patients who were so ill that no form of therapy was likely to be successful, and/or whose disease process had progressed to a point where the intervention proposed was no longer appropriate. With greater experience, the time window has diminished considerably; for instance, in a current trial of an novel anti-endotoxin therapy, only 8 h is allowed between onset of symptoms and administration of the drug. This is probably about as short as one get and still make the trial feasible.

Statistical issues

The nature of the disease process means that all phase III trials of novel agents in sepsis will be very large, multicentre, and usually international studies. This kind of study design has major implications in terms of the statistical analysis plan; these are summarised in Table 2 and are discussed in more detail elsewhere.

One aspect of this that merits brief comment is the notion of the ‘valid cohort’. The standard approach to analysing outcome in these trials has been to use the ‘intention-to-treat’ population. That is, all patients who were randomised to enter the study should be evaluated irrespective of whether they in fact represented a ‘realistic’ or appropriate population in which to evaluate the drug, or indeed, whether or not they even received the allocated regimen. There is no doubt that methodologically, and
from a regulatory perspective, this approach is correct. However, it has been argued that, given we are working with such a heterogeneous population, it would be reasonable to ask, additionally, what would have happened if we restrict the analysis to a so-called valid cohort, i.e. patients described prospectively as fulfilling both the spirit as well as the letter of the entry criteria and in whom it would be reasonable to posit that the intervention under study might be effective. For instance, a patient with a ruptured aortic valve will not survive unless the valve is repaired; without surgery, it is not a ‘fair test’ of a drug aimed at TNF, for instance. While this is self-evidently true, the approach is obviously open to the criticism of post hoc analysis. However, it is possible to carry out this kind of evaluation in a blinded fashion and, while it can never replace a formal intention-to-treat analysis, it does provide an opportunity to form an opinion of whether the drug has any useful activity and perhaps to serve as a hypothesis-generator for subsequent studies.

**Outcome measures**

It has been suggested that one of the reasons for the failure of sepsis trials is that we have been using the wrong endpoints. The question of what we are trying to achieve with adjunctive agents for sepsis – and hence what we should be measuring – has been the subject of considerable debate. Death has much to commend it. It is an unambiguous, categorical endpoint which is easy to measure, and has obvious clinical and economic relevance. However it is not without its detractors. Difficulties arise, for example, with knowing when to measure to death, and dealing with the question of attributable mortality. Many have argued that requiring new agents to
produce a reduction in attributable mortality of 30–40% in such a complex disease as sepsis is simply unrealistic, and that alternative end-points, such as improvement in organ dysfunction scores are both more appropriate and more attainable. Another, related approach is to use one or more surrogate markers of outcome. This has been very useful in the field of HIV medicine where death was unsuitable as an endpoint because it was often long-delayed; however, in sepsis it is not at all clear which surrogate marker could be used. (For a recent and detailed discussion of this issue the reader is referred to the Proceedings of the Toronto Roundtable Symposium on Outcome Measures for Clinical Trials in Sepsis, published in full in Sepsis 1997; 1.)

**Conclusions**

There is no single, simple answer to the question of why so many clinical trials of new agents in sepsis have failed. It will be clear from what has been discussed in this paper that in some cases the explanations are clear, and might have been predicted. In other cases, there were entirely unexpected complications such as can occur in any clinical trial programme, and are essentially just ‘bad luck’. Finally, there are the difficulties which have become apparent in clinical trial methodology, about which we have learnt much in the last few years. Future trials in this area will be much better designed as a result of this experience.

The difficulties and frustrations of this programme have led some to suggest that we should abandon this approach altogether. I think that would be mistaken. The placebo mortality in recent clinical trials of sepsis has been about 40% – and that represents a very real clinical challenge. As Francis Bacon pointed out 400 years ago, we cannot afford to sit still and do nothing.

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