Current clinical controversies in the treatment of sepsis

J Cohen

Sepsis continues to represent an unmet medical need and is a major cause of morbidity and mortality in intensive care units. Recently four major new developments have been reported, each of which appears to have a significant beneficial effect. These are: the use of low dose steroids, early goal-directed therapy, intensive insulin therapy and drotrecogin alfa (activated). Despite early enthusiasm, in each case significant concerns and reservations have emerged. Here, these issues are considered and the current status of these treatments is discussed.

Introduction

Sepsis is widely perceived as an unmet medical need. Epidemiological studies from North America and Europe continue to show that sepsis is the principal clinical challenge on intensive care units, and that it is responsible for substantial morbidity and mortality.1-3

There is certainly no doubt that it also continues both to intrigue and frustrate clinicians and scientists in equal measure. Research into a better understanding of the pathophysiology continues unabated,4 and the extent of new knowledge that has emerged from these investigations is truly remarkable. Key among these have been the unravelling of the role of the coagulation cascade, the recognition of the neuro-inflammatory pathway,5 and perhaps the most significant of all, the understanding of innate immunity and the part played by Toll receptors and their downstream pathways.6 There has also been considerable activity among clinical scientists, and over the last five to 10 years several major innovations in the clinical management of sepsis have been introduced.7 Unfortunately, several of these developments - some would say, all of them - have not stood the test of time and the frustration lies in the fact that at least from some perspectives, we seem to have made little real headway.

Here, I want to describe the four major clinical innovations that have been introduced in recent years and discuss why clinicians are still uncertain about their long term value.

Physiological steroid replacement (‘low dose steroids’)

Background

The first major clinical trials of steroids in sepsis date back to the 1980s. A substantial body of pre-clinical 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 indeed very effective. Based on these findings, two large clinical trials of high dose steroids were conducted and both concluded that these dose regimens were not effective in preventing death from sepsis, or indeed, were perhaps even harmful, increasing the risk of superinfection.8-10

And there the matter largely lay for some years, until several investigators, notably Annane and his colleagues, suggested that septic patients might be functionally Addisonian, and that they might benefit from low dose (‘replacement’) steroids.11 The hypothesis advanced by these investigators was that some septic patients failed to respond adequately to the physiological ‘stress’ that occurs in sepsis. Based on pilot data in which small doses of hydrocortisone reduced vasopressor dependency, they proceeded to carry out a prospective, randomised controlled trial in which patients with septic shock received replacement doses of hydrocortisone (50 mg every six hours) plus fludrocortisone (50 µg daily) or matching placebos, for seven days.12 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 corticotrophin test. There were fewer deaths in the active treatment group: 73 versus 60, hazard ratio 0.67, p=0.02. The findings were welcomed as demonstrating that a cheap and simple treatment could substantially reduce the likelihood of death in very ill patients with septic shock.

Concerns

The concerns that have emerged surrounding this approach can be summarised as four questions:

Do we know who to give them to? The hypothesis upon which Annane and others have developed this treatment is that a corticotrophin assay can identify a population of ‘non-responders’ for whom additional low dose steroid replacement would be beneficial. Even discounting the inconvenience of needing to do this in ‘real time’ and get a rapid answer from the laboratory, the data from the pivotal trial were not absolutely clear about the need for this step, and some endocrinologists have argued that the interpretation of the corticotrophin assay in this setting is far from straightforward.13-15 Indeed, some authors have interpreted the data to say that a CRH assay is not required.16

J Cohen, Professor of Infectious Diseases, Brighton & Sussex Medical School.
Correspondence to: Office of the Dean, BSMS, University of Sussex, Falmer BN1 9PH
E-mail: j.cohen@bsms.ac.uk

South Afr J Epidemiol Infect 2007; 22 (4):103-106
Do we know what dose regimen to use? The debate here revolves around the need for fludrocortisone, as used in the Annane paper. There is no convincing rationale for its use, yet the principal study demonstrating a beneficial effect of steroids did include a mineralocorticoid in the regimen.

Do we know it is safe? In the high dose steroid studies superinfection proved to be a significant concern. It was hoped that the much lower doses of hydrocortisone used in the new regimen would be safe and that is probably true, although there have been some concerns that even low dose steroids might play a role in reactivation of some herpes viruses, and/or that it might increase the risk of steroid-related myopathy and hence make extubation more difficult. There is no clear evidence at present that either of these are major concerns.

Do we know they work? The more particular question is, do they work in the ‘general’ ICU population, because close inspection of the Annane paper reveals that this was a very highly selected population of extremely sick patients, not entirely typical of the ‘average’ septic patient in most general ICUs. To try and answer this question, the European Union funded a trial to look at the role of low dose steroids (without fludrocortisone) in patients with sepsis and moderately severe septic shock. This study, the CORTICUS trial, has recently finished and preliminary data have been presented. In brief, the trial did not find evidence to support the widespread use of steroids in the population that was studied. The study found no effect on 28-day survival or shock reversal, although there was an effect on time to shock reversal (C Sprung, personal communication, 2007). Although we must wait for the full details to be published, these results cast serious doubt on the widespread applicability of low dose steroid therapy.

Early goal-directed therapy

Background

Exactly how to define - and measure - shock has been the subject of prolonged and sometimes heated debate, and the matter is certainly not yet resolved. When physiological measurements first started to become available in ill patients, it was learnt for example that basal oxygen consumption rose in ill patients, that there was dissociation between oxygen delivery and oxygen consumption, and that cardiac output often fell, and that this was related to a poor outcome. More detailed measurements made it possible to distinguish survivors from those who would die, and during the 1980s several investigators, notably William Shoemaker, suggested that outcomes would be improved by manipulating haemodynamic variables to some predefined targets. Attaining a cardiac index greater than 4.5 l/min/m², oxygen delivery index greater than 600 ml/min/m² and oxygen consumption greater than 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. The most recent recommendations now define shock on the basis of tissue dysoxia, and indeed, hypotension is not even regarded as a sine qua non of shock.

It was against this background that in 2001 Rivers published a startling paper in which he described the effects of ‘early goal-directed therapy’ (EGDT) used for the first six hours after patients presented in the Emergency Room with sepsis. In a prospective, randomised controlled trial in 263 patients, the in-hospital mortality was 30.5% in the treatment group versus 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 ScVO₂ were monitored and manipulated with fluids or vasoactive drugs to achieve pre-defined endpoints.

Concerns

EGDT is apparently a cheap and (relatively) simple means of substantially reducing the mortality of sepsis, and indeed several recent consensus meetings have supported this approach. However, a number of concerns have been raised that will need to be addressed. The first is simply that the study should be repeated and confirmed in a more general setting. Rivers and his colleagues carried out their research in a single centre with a group of highly dedicated physicians. To what extent can these findings be extrapolated to a wider, non-specialist environment? Secondly, how representative was the population that Rivers studied? An overall placebo mortality of 46% is much higher than many would anticipate for a ‘general’ population of patients with sepsis (typically nearer 30%). And finally, how generalisable is the Emergency Room setting in which the Rivers study was done, since this is not necessarily a healthcare model that exists in many places outside North America.

Tight glycaemic control

Background

Hyperglycaemia associated with insulin resistance is well documented in critically ill patients, and data from trials in patients with acute myocardial infarction suggested that controlling high blood sugar improved the outcome. In 2001, Van den Berghe et al published the results of a trial comparing the mortality of critically ill surgical patients in whom blood sugar levels were tightly controlled with insulin infusions to achieve a target blood glucose of 4.4-6.1 mmol/l, to patients receiving conventional treatment in which the blood sugar was maintained at 10.1-11 mmol/l. The trial was stopped after 1,548 patients had been enrolled because the mortality in the experimental arm was 4.6% compared to 8% in the conventional arm, a relative reduction of 32%, p<0.04. Once again this seemed to be a cheap and remarkably simple way of substantially reducing mortality, and the strategy was widely adopted. Very quickly though commentators observed that it may not be appropriate to extrapolate these findings to all septic patients in ICU, in particular because it was obvious that this population of ‘critically ill surgical patients’ with a placebo mortality of just 8% was very different to the typical septic patient in a mixed medical-surgical ICU, of whom perhaps 30-35% would be expected to die. In response to these criticisms Van den Berghe went away and repeated her study, this time in the medical ICU. The results were interesting, but not quite so clear cut. This time, the placebo mortality was right on target, 40%. The mortality in the treatment group was 37.3%, a difference that was not significant. However, in patients who stayed in the ICU for three or more days there was a significant reduction in mortality (from 52.5 to 43%, p=0.009), while for the 433 patients who were in ICU for less than three days, mortality was greater in the intensive insulin arm. The problem was...
that it was not possible to identify, in advance, which patients would be in the unit for more than three days and therefore potentially benefit from the treatment.

Concerns

Not surprisingly this paper has raised a number of concerns.25 These centre around the fact that the second study failed to confirm the clear-cut benefit of the first trial, that these are single centre studies that may not be easily rolled out to a general ICU population, and that the investigators used a rather unusual feeding regimen that might have affected blood sugar levels. A potentially much more significant concern is that the need for extremely tight glucose control runs the risk of significant and symptomatic hypoglycaemia, indeed something that Van den Berghe encountered although the fact that there was a dedicated trial doctor mitigated the possible risks. However, of greater concern is the result of the SepNet study carried out by German investigators, who attempted to reproduce the findings in a multicentre trial. This trial was suspended because there was a significant increase in hypoglycaemia in the treatment arm (12.1 vs 2.1%) and no evidence of a reduction in mortality;26 the full details of the study have not yet been published.

There is now a significant cloud hanging over this approach and most ICUs have suspended the effort to bring the glucose down to ‘Van den Berghe’ levels, although appropriate glucose control is still part of standard care.

Drotrecogin alfa (activated) [activated protein C]

Background

It is not my intention to review here the extensive pre-clinical and clinical development programme that lies behind the introduction of this drug (Xigris®) as the only licensed adjuvant therapy for sepsis (see20 for reviews). In the UK, NICE (the National Institute for Clinical Excellence, an independent body which evaluates treatments to determine if they should be available on the National Health Service) concluded that drotrecogin alfa (activated) should be “recommended for use in adult patients who have severe sepsis that has resulted in multiple organ failure (that is, two or more major organs have failed) and who are being provided with optimum intensive care support”.21 The introduction of drotrecogin alfa (activated) was based on a single, large, placebo-controlled trial (PROWESS) that was stopped prematurely by the Data Safety Monitoring Board on the grounds of efficacy.22 Yet the use of this drug is the subject of almost unprecedented controversy and debate; why so?

Concerns

The scientific concerns about the benefits of the drug can be summarised as follows:

- The lack of a confirmatory study in the same population
- The fact that there was no independent validation of the severity index (an APACHE II score of 25 or more) suggested by the US FDA as the group who would most likely benefit from the drug (and indeed, note that the European regulatory agencies adopted a different approach, as evidenced by the UK NICE advice, noted above)
- The failure of two further studies to demonstrate any benefit: the ADDRESS trial27 in early sepsis, and RESOLVE,28 carried out in children with sepsis. Of further concern was the lack of benefit seen in the subset of ADDRESS patients who were in fact identical to the patients in PROWESS, although of course ADDRESS was not powered to detect such an effect.

Laid on top of these legitimate scientific questions is a second order debate (equally legitimate but different) about the role that pharmaceutical companies have had in attempting to influence academia to advise or recommend their drugs.29

What is clear is that without further confirmatory data this debate will not go away. Thankfully this now seems likely to happen. Two industry-sponsored trials will shortly begin, one aimed at the high-risk population identified in PROWESS and the other in which the dose regimen of the drug will be modified to better reflect the consumption of the active principal in the patient. Perhaps even more importantly, the French government has agreed to sponsor an independent, second study in an attempt to confirm the results of PROWESS. These trials will all take several years to complete but they are essential if we are to really understand if this drug has a role in the treatment of sepsis.

Conclusions

It is perhaps not surprising that it has been difficult to make progress in a field that is so highly complex - both in terms of its pathophysiology and its clinical manifestations. It is no accident that an international consensus group that met to try and ‘improve’ the diagnosis of sepsis could not even agree on the terminology.30 The Surviving Sepsis Campaign has published guidelines recommending best practice in the clinical management of sepsis31 and these will shortly be updated, but the equivocation that they reveal in terms of many of the most basic aspects of treatment speaks volumes about the lack of a solid evidence base in this area. All the more reason to press ahead with both basic and clinical science.

References

11. Thys F, Laterre PF. Hydrocortisone in septic shock: too much, too little,

Sepsis treatment controversies


