

Meeting report

Blending science and compassion: The 30th educational symposium of the Society of Critical Care Medicine, San Francisco, USA, 10–14 February 2001

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Introduction

This year's symposium was dominated by two major themes. The first was the unveiling of the results of the phase II clinical trial on the use of recombinant human activated protein C (rhAPC) in the treatment of sepsis. For the first time in 30 years a major breakthrough has been achieved and the result is all the more welcome given that recombinant antithrombin III was recently shown to be of no use in the treatment of sepsis. The second major theme was the need to educate physicians in the nuances of patient outcome in the intensive care unit (ICU). For a long time the philosophy has been to treat the patient as an object to be repaired. Now, however, we have the ability to prevent death in the majority of cases, but to what end? Statistics from the USA show that about 20% of patients admitted to the ICU die there. The important point is that 70 to 90% of those deaths are the result of a conscious decision to withhold or withdraw treatment. The issues of quality of life after treatment, and at the end of life (in the ICU) were also discussed.

Results of the Phase III rhAPC multicentre placebo controlled trial: Presented by J-L Vincent, G Bernard, D Angus, and S La Rosa

As researchers have refined their understanding of the many biochemical pathways involved in sepsis, they have identified new targets for developing potentially effective treatments. So far, the search for drugs has been a frustrating one. More than 30 clinical trials of investigational compounds for the treatment of sepsis have been performed, but none have produced a safe and sufficiently effective therapy. The most recent failure was with anti thrombin III (AT3). However, recombinant human activated protein C (rhAPC) has the potential to be the most significant step forwards in the treatment of sepsis since the introduction of antibiotics in the 1930s.

Trial Design

PROWESS (Protein C Worldwide Evaluation in Severe Sepsis) was a prospective, double blind, placebo controlled trial investigating the effectiveness of rhAPC in reducing the mortality of patients with severe sepsis. 1690 patients were recruited from 11 countries. To qualify patients had to have 3–4 criteria for Systemic Inflammatory Response Syndrome (SIRS), failure of at least organ, and were not at high risk for bleed events. They were randomised to receive either placebo or rhAPC administered as a continuous infusion of 24 µg/kg/h for 96 h. The primary end point was 28 day all-cause mortality (*P* value derived from a Cochran-Mantel Haenszel test, stratified for APACHE II score, age, and baseline Protein C activity).

Results

Analysis of subgroups revealed that the response to rhAPC was consistent across all patient criteria (Table 1). The survival curve showed that rhAPC had an effect after only 2–3 days. One area of concern was the possibility of serious bleed events. This was defined as an intracranial bleed, any other life threatening bleed, or a bleed that required more than 3 units per day of packed red blood cells for two consecutive days. The incidence of serious bleed events was not statistically significant. Biochemical analysis indicates that rhAPC had an effect regardless of whether the patients were deficient in protein C. Indeed, the biochemical analysis indicates that rhAPC acts in a complex and synergistic manner – both anti-thrombolytic and anti-inflammatory properties can be clearly demonstrated. rhAPC may increase the odds of survival, but if a patients who would have died simply survives in a moribund state, then the benefits of the drug are questionable. However, this is not the case. Treatment with rhAPC had no adverse effect on morbidity.

Table 1

Treatment with rhAPC: survival rate, risk of death and side effects		
	Placebo <i>n</i> = 840	rhAPC <i>n</i> = 850
28 day mortality	30.83%	24.77%
Relative risk of death	Not applicable	19.43% reduction
Survival odds	Not applicable	38.1% increase
Serious bleed event	2.0%	3.5% (<i>P</i> = 0.06)

Conclusions

Treatment with rhAPC reduces mortality in patients with severe sepsis with minimal serious side effects and an acceptable risk benefit profile. After decades of research, a treatment tool for severe sepsis appears to be just over the horizon.

(This paper is to be published in the 8 March 2001 issue of the *New England Journal of Medicine*. Due to its possible clinical implications, it has been on early release on their website since 9 February 2001 [www.nejm.org].)

Pro/Con debate on the use of steroids in sepsis: D Annane, J Luce

John Luce opened the debate by presenting a synopsis of 30 years of research into the use of short-term steroids in the early treatment of sepsis (see Table 2).

Based on the evidence in Table 2 and backed up by two meta-analyses [8,9], John Luce took the stance that early treatment with steroids has no effect on mortality, and that any new thinking on the effectiveness of steroids in patients with sepsis has to address the weight of evidence collected to date.

Table 2

Summary of the major studies on the use of steroids in the treatment of sepsis		
Author	Treatment protocol	Outcome
Klastersky J <i>et al</i> 1971 [1]	Betamethasone 1mg/kg for 3 days	No difference in mortality
Schumer <i>et al</i> 1976 [2]	2 part study: Part 1 (prospective study): dexamethasone 3 mg/kg or methylprednisolone 30 mg/kg or placebo Part 2 (retrospective study) dexamethasone or methylprednisolone or placebo	Decrease in mortality Decrease in mortality
Lucas and Ledgerwood 1984 [3]	Dexamethasone 6mg/kg for 48 h	No difference in mortality
Sprung <i>et al</i> 1984 [4]	Methylprednisolone 30 mg/kg, dexamethasone 6 mg/kg	Decrease in mortality
Bone <i>et al</i> 1987 [5]	Multicentre study Methylprednisolone 30 mg/kg 4 doses over 24 h	Increase in mortality
Hinshaw <i>et al</i> 1987 [6]	Methylprednisolone 30 mg/kg	No difference in mortality
Luce <i>et al</i> 1988 [7]	Methylprednisolone 30 mg/kg 4 doses over 24 h	No difference in mortality

Djelali Annane took the rather unusual step in a pro/con debate of agreeing with John Luce, stating that high dose, short course steroid treatment is not a viable option for the treatment of sepsis. Instead he championed replacement treatment (compensating for diminished hormone levels) in dealing with patients suffering from adrenal gland dysfunction as a good approach to dealing with septic shock. He presented data from a series of studies that seem to indicate that low doses of hydrocortisone for longer periods apparently decrease inflammation, nitrous oxide activity, and adhesion molecule levels. In addition, there is evidence of trends towards reversing septic shock, improving organ function over time, taking patients off vasopressor support faster, and increasing survival rates. Whilst these results are encouraging, they are the result of small-scale studies.

Djelali Annane then presented his own results from a randomised placebo controlled trial of 299 (149 study group: 150 placebo) patients with sepsis. The results showed an increase in survival in all patients treated with low dose, long treatment hydrocortisone. The increase in survival rate was more marked in patients with some adrenal insufficiency. The data was received quite well but with the reservation (shared by the presenter) that whilst the results may look good, they are not a strong enough for intensivists to return to giving steroids to patients with septic shock. More evidence is required and on the basis of these results large-scale studies should be undertaken.

Sepsis in the critically ill – back to the future: Jonathan Cohen

"We are overwhelmed with an infinite abundances of vaunted medicaments, and here they add a new one."
Thomas Sydenham (1624–1689)

Jonathan Cohen chose to open his plenary speech with this quote to illustrate that, although the treatment of

sepsis has probably taken a quantum leap forward with the results of the PROWESS trial, the search for new treatments should not be considered unnecessary.

The conventional paradigm of sepsis is being superseded by the realisation that there are a variety of routes that lead to what we term sepsis. The natures of the infective organisms – Gram-positive, Gram-negative or a combination of the two – help to determine the nature of the clinical response, which in turn is modified by the genetic makeup of the individual. The type of infection will also affect the extent of inflammatory mediator release, in turn determining organ specific dysfunction as well as specific adaptive and innate immune responses. The concept of initiating different treatments according to the route by which a patient's sepsis is caused is a significant step away from the idea of a 'one treatment fits all' approach.

What targets could a tailored treatment be based on? For Gram-negative bacteria, endotoxin is an immediate candidate. The use of antibodies aimed at the components of lipopolysaccharide (LPS) might be one approach. LPS agonists are another. One possibility is to target LPS binding proteins, such as serum amyloid protein (SAP). A recent paper in the *Proceedings Of The National Academy Of Sciences of the United States of America* [10] showed that mice genetically altered to be deficient in both copies of the SAP gene appeared to be protected from the effects of endotoxin. It appears that SAP inhibits bacterial phagocytosis. Compounds exist which inhibit SAP/LPS binding [10], and time will tell whether their potential can be realised.

Gram-positive bacteria can also be targeted specifically. We know that their cytokine stimulation profile is different to that of Gram-negative bacteria, and there are also differences in the signal transduction pathways they use. Potential targets include their cell wall components (peptidoglycan and lipoteichoic acid), and extracellular products such as superantigen. Dr Cohen presented results showing that it might be possible to treat sepsis by removing superantigen from the circulation. There is a superantigen adsorbing fibre available, and *in vitro* studies show that it can reduce the stimulation of peripheral blood mononuclear cells (PBMC). Some very preliminary results with a rat model show that in principle, *in vivo* adsorption of superantigen is also possible.

At a recent UK Medical Research Council (MRC) international workshop on clinical trials in patients with sepsis or septic shock, the following suggestions were proposed:

1. Inclusion criteria – there must be evidence of a particular infective agent
2. There should be a test for biological plausibility – does the treatment being tested stand a reasonable chance of working given the nature of the patient's sepsis?

3. Severity criteria – The results will be skewed if the patient belongs to either extreme of the severity curve (ie about to die or not very ill).

These proposals are currently in press and will be published in *Critical Care Medicine*.

In conclusion, Dr Cohen argued that, although the effectiveness of rhAPC should not be understated, we should not consider that it represents a panacea for the treatment of sepsis. Neither should we fall into the trap of thinking like Thomas Sydenham. It is not the beginning of the end of sepsis research, but the end of the beginning.

For a related commentary in this issue by Martin Llewelyn and Jonathan Cohen, see [11] and <http://ccforum.com/content/5/2/053>.

Measuring outcomes in critical care: D Angus, J Marshall, D Hyland and J Randell Curtis

After the excitement of the PROWESS trial results, attention returned to the second major theme of the symposium, namely the need for a shift from the short-term aim of patient survival (via aggressive management strategies) to the long-term assessment of outcome in patients treated in the ICU. As treatment technologies become ever more effective at preventing the patient from dying in the ICU, there is a need for the technology to be assessed in terms of quality of life (QOL). Long-term QOL assessment is not usually part of the design of randomised controlled trials (RCTs). Typically, outcome is measured at day 28. The need for a closer examination of the long-term prognosis of patients is important both from an economic point of view and the wishes of the patient and his/her family.

Economic outcomes: Derek Angus

Derek Angus looked at the means and implications of applying a cost effectiveness assessment (CEA) to a technology. While the budget for health care reaches a ceiling, the number of new treatments continues to increase making it important to compare treatment regimes so as to make the best use of funds. There are two questions; is this new therapy worth using compared to existing therapies, and should the resources be made available for this therapy? There are three ways of making the assessment:

1. Cost minimisation – is treatment A cheaper than treatment B?
2. Cost benefit – what is the cost of a life for this treatment?
3. Cost effectiveness – the value of a life saved or the improvement in QOL?

Deriving figures with the first two methods is simple, but the usability of the data is questionable. The third method is probably the best way of looking at treatment effectiveness but the model used to calculate the effec-

tiveness of a treatment must be robust if the figures are to have any value.

When comparing two treatments, one can consider a graph in which the X-axis represents positive and negative cost values (ie increases or decreases in expenditure) and the Y-axis represents the effect of a treatment (positive values: better effect, negative values: worse effect). If the results of a treatment are plotted on this graph then they will lie in one of four basic areas: Cheaper and more effective, more effective but more expensive, cheaper but not as good or more expensive and not as good. It must be remembered that although a point may be plotted on this graph, one cannot be certain about the cost, and the effectiveness will not be a point value either. One must therefore define the effectiveness of a treatment in terms of an area to be plotted on the graph.

It is important that QOL be assessed when performing these types of calculations. It is questionable whether a treatment that saves a life but leaves the patient with a poor QOL represents an improvement. From a purely economic point of view one must consider the cost of the treatment required by a patient saved by the new technology, but then requiring additional expenditure due to their low QOL (eg renal failure requiring permanent dialysis). Quality adjusted survival is important in treatment assessment.

Different technologies need to be assessed using similar measurements to allow true comparisons. Close attention needs to be paid to the costs that are being measured. 28 day survival is the typical outcome measure in an RCT but long-term costs (such as dialysis) are important, and there is the matter of 'patient well being', a subjective but important consideration.

A well-constructed CEA, applied carefully, can be an effective tool in determining the appropriate treatment options. It should not be used as a rationale to withdraw or withhold treatment. Hopefully recombinant human activated protein C represents a treatment regime that will be deemed to be truly effective. As a new technology, it is likely to have a substantial cost attached to it, but hopefully the long-term assessment will be that it does indeed represent an effective treatment for sepsis.

Assessing morbidity: John Marshall

How do we measure morbidity? How do we combine morbidity and mortality assessment to arrive at a useful outcome measurement? These were two questions posed by Dr Marshall. He listed four morbidity measurements:

1. Length of stay (LOS)
2. Complications
3. Physiologic derangement
4. Interventions

LOS is a valid measurement of morbidity, but it is strongly affected by practice and is physician controlled. Complications vary in relation to the clinical problem, are again dependent on practice patterns, are many in nature and need to be objectively defined. Using multiple organ dysfunction syndrome (MODS), sepsis-related organ failure assessment (SOFA), and other outcomes for measuring organ dysfunction represent the first steps to quantify physiologic derangement. Interventions need to be defined and weighted in some manner. Again they are practice dependent.

Pre-existing conditions should also be disassociated from those that develop during treatment. Studies have shown that pre-existing conditions strongly define patient outcome. These are difficult to alter. Dysfunction that occurs post treatment can, in theory, be altered, so it is this that the intensivist should try to measure.

The best outcome measurement is probably a combination of morbidity and mortality measures. Such a tool would be a sensitive and instructive measure of outcome. Morbidity measurement has been neglected and this must be altered if a true outcome measurement is to be devised.

Moving beyond survival: Daren Hyland

Daren Hyland chose to look at expanding quality of life measurements to try to encompass criteria currently not used in the definitions currently used in the ICU. Health related quality of life is not just about survival. Instead it is a component of two items: firstly, the objective measurements of health status as defined by level of dependence on long term medical support; and secondly, on the subjective, society-assessed 'quality of life' of an individual. Attempts to extend the QOL criteria beyond those of the ICU have infrequently been done, are of poor methodological quality, and use a variety of tools. One of the key requests made by Dr Hyland was for randomised controlled trials to address the question of how far back to a baseline QOL a patient might get. Again, when looking at the PROWESS results, this is a question for which there is simply no data.

Outcome at the end of life: J Randell Curtis

J Randell Curtis drew attention to the difficulties of assessing the quality of care that occurs at the end of life. In the USA, the majority of ICU patients that die, do so as a result of the decision to withhold or withdraw care, so there is a need for objective measurements of standard of care. The needs of the patient, their family, and those of the nurses and physicians have to be taken into account. For obvious reasons, it is unlikely that an investigator can get any patient assessment of the standard of their care. The question then is whether the tools used to measure quality of care are measuring it from the point of view of

the family, or the care team. There are some tools available, such as those developed by Wasser and co-workers [12]. Dr Curtis also drew some attention to a questionnaire that he and his team had developed in an attempt to get to grips with these issues. His final point was a request for more research to be done to generate a valid outcome measure at the end of life.

Summary

In 2000, the SCCM chose to concentrate on the blaze of new technology at the dawn of a new century. Twelve months later, the focus has turned to assess these technologies, not just in terms of what can be achieved with a patient, but also when, or if, that treatment should be applied.

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