

Meeting report

The 21st International Symposium on Intensive Care and Emergency Medicine, Brussels, Belgium, 20–23 March 2001

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Abstract

The 21st International Symposium on Intensive Care and Emergency Medicine was dominated by the results of recent clinical trials in sepsis and acute respiratory distress syndrome (ARDS). The promise of extracorporeal liver replacement therapy and noninvasive ventilation were other areas of interest. Ethical issues also received attention. Overall, the 'state of the art' lectures, pro/con debates, seminars and tutorials were of a high standard. The meeting was marked by a sense of renewed enthusiasm that positive progress is occurring in intensive care medicine.

Keywords: ARDS, ethics, hepatic failure, non-invasive ventilation, sepsis

Introduction

This year's symposium was dominated by the results of recent clinical trials. After 10 years of 'magic bullet' trials in sepsis, a number of successful therapeutic options are now emerging. In addition, recent advances in our understanding of the soup of mediators observed in sepsis offer yet more tantalizing targets for new therapies.

In contrast, the eagerly awaited results from Italy of the prone positioning trial in ARDS were disheartening. The epidemiology of both sepsis and ARDS, and their impact on clinical studies and the future provision of critical care were also hot topics. The era of extracorporeal liver replacement therapy is upon us, with considerable early promise and the probability of wide availability. Finally, as always, ethics remained an area of interest.

This report summarizes and discusses the presentations on the above topics.

Sepsis

Angus (Pittsburgh, PA, USA) presented his group's work on the epidemiology of sepsis in the USA (accepted for publication in *Critical Care Medicine*). They developed a method for identifying hospitalized patients with sepsis based on ICD9 criteria, the most widely recorded coding system used in US hospitals. Prospective testing of the method found it to be both sensitive and reliable. They then applied it to a representative selection of US hospitals. Their results indicated that about 50% of intensive care unit (ICU) patients have systemic inflammatory response syndrome, and that approximately 20% of these progress to severe sepsis. Mortality for severe sepsis was greater than 30%. Demographically, those at the extremes of age represent the most at-risk groups, in whom the mortality is also the highest. These data provides yet another reminder that the increasing demands on health care resources caused by the ageing population is predicted to exceed intensive care provision within the next

10–20 years. Finally, those investigators found a striking demographic peak in patients aged 20–30 years, which they attributed largely to human immunodeficiency virus.

The long-standing debate between the two schools of sepsis theory – microcirculatory dys-autoregulation versus cellular dysfunction – shows signs of resolution. New techniques for studying tissue oxygen tension, presented by Ince (Amsterdam, The Netherlands), provide more evidence that microcirculatory dys-autoregulation results in significant shunting. This occurs predominantly in the submucosal and serosal portions of organs, and is an early event. These studies show that the macroscopic restoration of global oxygen delivery fails to improve oxygen consumption as the mucosa becomes hyperoxic, whereas the submucosa and serosa remain hypoxic. Somewhat counterintuitively, this can be reversed in the face of resistant hypotension with vasodilators, at least in animal models.

The cellular dysfunction camp, although still somewhat doubtful as to the importance of these microcirculatory findings, have now clearly established that their championed mechanism of mitochondrial failure is a late but crucial event in the evolution of sepsis. Fink (Pittsburgh, PA, USA) presented evidence that mitochondrial failure in septic cells is triggered by the activation of the enzyme poly-adenosine diphosphate ribose polymerase [1]. This enzyme represents a significant target for novel therapies, which are apparently already in development. The debate regarding the toxicity of oxygen and the formation of free radicals continues despite the absence of demonstrated effectiveness of scavenging therapies, and is a testament to the incomplete understanding of this area.

The round-table conference preceding this year's symposium concentrated on distilling current knowledge on the microscopic events in critically ill patients into an explanation of the macroscopic multiorgan failure that is so commonly encountered. The conclusions of the conference appeared to relate mostly to future directions for research, in particular the study of organ–organ interactions. Marshall (Toronto, Canada) proposed the development of an alternative to the much-maligned physiological scoring systems, based on the staging systems widely used in the field of oncology. He proposed that mediator levels, in addition to physiological variables, will soon be used usefully to characterize septic patients. He also suggested that, in the light of the recent successful mediator trials in sepsis, future therapies will be directed in a manner analogous to the control of glucose in diabetic patients.

The natural anticoagulants antithrombin III (AT III), tissue factor pathway inhibitor (TFPI) and activated protein C (APC), and the cytokine tumour necrosis factor (TNF)- α are the latest inflammatory mediators to be targeted in

large multicentre clinical trials in an attempt to improve the current dismal outcome for patients with severe sepsis.

The KyberSept AT III study recruited over 2300 patients from 200 centres, with high Simplified Acute Physiology Scale scores (median 50), and a mortality of nearly 40% [2]. Unfortunately, no overall benefit was shown between AT III and placebo, although results were more encouraging in an analysis of the subgroup of patients who received AT III but no heparin, which is known to inhibit AT III. Interestingly, improvements in quality of life scores were seen in survivors who received AT III in comparison to those who received placebo, suggesting that morbidity may be reduced, although again this was an analysis of a subgroup. Patients in the AT III group who received concomitant heparin had a significantly higher incidence of bleeding events, and outcome worsened as the dose of heparin increased. Explanations for the failure of this study included the inhibitory effects of heparin and the failure to achieve AT III activity levels of greater than 200% from baseline in the treatment population, a level established as required for therapeutic benefit in phase II trials.

Phase II clinical trial results using TFPI (TFPI $n=141$, placebo $n=69$; unpublished data) show a mortality benefit in the sicker sepsis patients who already have coagulation problems. Results of the phase III multicentre study are expected to be presented at the 22nd International Symposium on Intensive Care and Emergency Medicine, in Brussels in 2002.

Human trials of various anti-TNF- α formulations have been variable to date, and include North American sepsis trial (NORASEPT) I [3], International sepsis trial (INTERSEPT) [4] and NORASEPT II [5]. Possible reasons have included a lack of biological activity of the anti-TNF- α formulation studied, inappropriate timing of therapy, redundancy of proinflammatory mediators and heterogeneity of patient populations. The Monoclonal Anti-TNF, A Randomized controlled Sepsis Trial (MONARCS) study used a different anti-TNF- α formulation (F[ab']₂ fragment of a murine monoclonal antibody to human TNF- α), and stratified patients based on demonstrable abnormalities in immunological pathways (highly elevated interleukin-6 levels – a circulating cytokine that is induced by TNF- α). Unpublished results revealed 28-day mortality rates of 44 and 48% in the anti-TNF- α and placebo groups, respectively, in those patients who had high interleukin-6 levels on recruitment to the study ($n=488$ anti-TNF- α , $n=510$ placebo). This represented a relative mortality reduction of 14%. Relative mortality reduction in all patients ($n=1305$ anti-TNF- α , $n=1329$ placebo), independent of baseline interleukin-6 levels, was only 10%.

The Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study is hot off

the press [6], and presentation of the results at the congress allowed those of us who still carry the unopened *New England Journal of Medicine* issue in our briefcases to catch up! A total of 164 sites from 11 countries recruited 1690 patients with severe sepsis, before the trial was prematurely stopped following the second safety analysis. Twenty-eight-day all-cause mortality rates for placebo and APC were 31 and 25% respectively, with a relative risk reduction of 19%. Resolution of cardiovascular and respiratory function was more rapid in survivors who received APC, although ICU and hospital stay did not differ. There was a trend towards an increase in serious bleeding events in the APC group (3% APC versus 2% placebo), but these events were primarily due to trauma or instrumentation. Although this is an exciting breakthrough, we all recognize that when APC reaches the market place it will seriously stretch ICU finances, especially because there appear to be other mediators on the horizon that we will be encouraged to use, in combination, to fight the inflammatory 'soup'.

Acute respiratory distress syndrome

Two opposing epidemiological views of ARDS were presented by Lemaire (Créteil, France) and Evans (London, UK). Broad agreement does seem to exist as to the incidence of this condition, which is in the order of 10/100,000, although there is significant variation between countries. It was argued that this variation results from the availability of ventilated beds, with higher incidences apparent in countries with greater provision, emphasizing that this condition can be considered the result of intensive care intervention or, as one speaker put it, 'physician-induced lung injury'.

Early results from the Acute Lung Injury Verification of European Epidemiology (ALIVE) study (unpublished data), sponsored by the European Society of Intensive Care Medicine, are at odds with recent trial findings. The ALIVE study, which included over 6000 patients surveyed in 1998, found a 50–60% 28-day mortality, which compares to only 20–30% in the control groups of recent trials. Pneumonia was the commonest cause, responsible for 50% of cases, with sepsis identified as the cause in a further 20–30%. Astonishingly, this study found the ratio of arterial oxygen tension to fractional inspired oxygen at ICU admission was highly predictive of mortality, despite continuing controversy regarding this measurement.

A diverse range of views were presented from the Third International Consensus Conference on ARDS (unpublished data), held in Barcelona late last year. The decision as to how to change the defining criteria for this condition remains unresolved. The debates surrounding chest X-ray criteria, the use of the ratio of arterial oxygen tension to fractional inspired oxygen, and the level/utility of pulmonary artery wedge pressure measurements continue.

In addition, a debate has arisen as to whether ARDS can be a unilateral process, and whether it can coexist with cardiac failure. There appears to be increasing recognition that ARDS represents only a small subset of patients with acute lung failure (approximately 30%). Surprisingly little is known about the remainder of this larger group. In contrast to the ALIVE study, several centres have reported their 28-day mortality at 40%, which represents an improvement from the 60% of 10 years ago. However, it was argued that a 28-day follow-up period is too short for clinical trials, as the long-term quality of life for patients with ARDS is poor compared with that of critically ill patients without this condition. Results suggest that the recovery of lung function is good overall, but is dependent on severity. Treatment recommendations include the universal adoption of the US National Institutes of Health protective lung ventilation strategy [7]. There was general agreement that recruitment manoeuvres are beneficial, but how and when to employ them remains controversial.

Rouby (Paris, France) put forward a new classification for ARDS based on computed tomography findings. He observed that patients can be split into three groups, depending on the appearance of the upper lobes. In group 1 the upper lobes are normal, and positive end-expiratory pressure (PEEP) is of little benefit and results in significant over-distension. Survival in this group is approximately 60%. In group 2 the upper lobes are abnormal, PEEP is of dramatic benefit, but survival is only approximately 25%. In group 3 there are mixed/patchy abnormalities, the effects of PEEP are less predictable, but, as in group 1, survival is approximately 60%.

Gattinoni (Milan, Italy) presented the results of the long-awaited Italian multicentre randomized controlled trial of prone positioning in ARDS (unpublished data). This trial was terminated after 3 years despite having only recruited 304 patients; enrollment of 750 patients was originally planned, in order to achieve sufficient statistical power. At trial outset, recruitment was encumbered by the lack of familiarity with and scepticism regarding this procedure in many of the centres. However, by the end of the study many participants were unwilling to enter patients into the trial, because they felt it unethical to deny them this intervention. The trial protocol resulted in patients in the treatment group being prone for an average of only 7 out of 24 h for a 10-day period. Overall there was no difference in mortality between the control and treatment groups at day 10, time of ICU discharge, or at 6 months. Interestingly, analysis of subgroups revealed a significant difference in the outcome at 10 days for patients with the most severe disease, although this disappeared by ICU discharge. In retrospect, the design of this ambitious trial was flawed by its failure to establish the optimal utilization of this manoeuvre.

Extracorporeal techniques for liver failure

The opening session reported that we are making progress in supporting the failing liver (Wendon, London, UK). Current optimism should probably be limited to extracorporeal methods, because the molecular adsorbent recirculating system (essentially extracorporeal albumin dialysis) has been shown to have beneficial clinical effects as well as improved survival in two small randomized controlled trials [8,9]. The equipment is familiar to all those who use dialytic therapies, and we will undoubtedly hear more about this system in the next few years.

Noninvasive mechanical ventilation

The slide of a patient reading the newspaper through a transparent helmet, while receiving noninvasive ventilation (NIV) resembled pictures of a NASA astronaut! However, it was reported to be well tolerated for prolonged periods, and significantly reduces the complications associated with NIV (pressure areas, tolerance of mask). The recent Consensus Conference [10] examined weaning aspects of NIV and emphasized the reduced weaning time and avoidance of reintubation, but called for more randomized controlled trials. Finally, although continuous positive airway pressure has been shown to be beneficial in pulmonary oedema, caution is still advised with the use of bilevel positive airway pressure because of the reporting of myocardial infarction in several studies. However, the groups studied were unmatched and starting points were different, so conclusions should not be drawn until randomized controlled trial results are available in this area.

Ethics

This was a well-attended session, which, according to Levy (Providence, RI, USA), was in complete contrast to the interest shown in the USA for the subject. Although there were few new data in the session, the emphasis on a strategy for lawsuits was welcome. Suggestions included statements from scientific societies at a national and international level, open reporting in medical files of decisions to withdraw or withhold treatment, and family involvement in decision making that will ultimately involve better media education.

Conclusion

The last day of this year's symposium was sadly abandoned by many due to the Belgian rail strike. Despite this, the usual convivial atmosphere, both in and around the congress, was as abundant as ever. Overall, the 'state of the art' lectures, pro/con debates, seminars and tutorials were of the usual high standard, although, yet again, access to many of the symposium's venues was limited by the lack of capacity of the secondary rooms. The 21st International Symposium was marked by a sense of renewed enthusiasm that real positive progress is occurring at the coal face of intensive care.

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