

Meeting report

What are the challenges of translating positive trial results in severe sepsis into clinical practice? A media roundtable debate, 18 March 2002, Brussels, Belgium

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Abstract

The clinical syndrome of sepsis is common, increasing in incidence and responsible for as many deaths annually as ischaemic heart disease. Two recent interventional trials have demonstrated that early recognition and intervention can result in dramatic reductions in acute (28-day) mortality. This roundtable discussion was convened to identify ways in which these recent advances could be translated into clinical practice. The first obstacle surrounds the woolly and confusing terminology surrounding 'sepsis' with the systemic inflammatory response syndrome (SIRS) model largely discredited. Overcoming this should facilitate wider recognition, not only among health care providers (in particular those working in acute specialties outside intensive care units [ICUs]) but also politicians and the general public. Such education is vital if early recognition and intervention are to be successfully implemented.

Keywords health resources, sepsis

This open discussion was arranged to raise awareness of the common clinical syndrome of sepsis and the apparent paradox between the successful development of the first modifying agent for this syndrome – recombinant human activated protein C (rhAPC) – and a perception that there may be slow uptake of its use by clinicians. The participants were as follows (see the appendix for affiliation details and research activities): Jean-Louis Vincent, Antonio Artigas, Jan Bakker, Tony Sherry and Michele Schroeder.

Background

Sepsis is considered to be a complex clinical syndrome resulting from infection that gives rise to systemic inflammation [1,2], although somewhat confusingly nonmicrobiological tissue injury can precipitate an identical clinical/pathophysiological picture. This is made all the more difficult as confirming the presence of infection in critically ill patients is often impossible [3]. When severe, sepsis syndrome manifests as multiple organ dysfunction and is associated with an approximately 30–50% mortality [4]. It is

perhaps the commonest condition presenting to intensive care clinicians and accounts for as many deaths as ischaemic heart disease or common cancers (Davies *et al.*, unpublished data). Recent epidemiological and health care economic surveys have estimated there to be 750,000 cases of severe sepsis annually in the USA, which will rise to over a million by the end of the current decade; at least 225,000 of these cases result in fatality, with the annual cost of treating severe sepsis in the USA estimated at \$17 billion [5]. In the European Union, the estimated number of fatal cases is 150,000 annually, and the cost of treatment \$6.7 billion (€7.6 billion) (Davies *et al.*, unpublished data). Sepsis syndrome has been, and remains, a major focus of intensive care research and the subject of a large number of international multicentre trials [6]. Despite these facts, there is limited awareness of the condition among the general public and health care providers. One of the explanations for this is felt to be the confusing definitions and terminology surrounding the condition [7], in particular the SIRS diagnostic criteria [8], which have been the standard

diagnostic tool employed, especially in therapeutic trials. However, SIRS has multiple deficiencies, not least that two of the criteria are met performing normal daily activities such as running for a bus (tachycardia and tachypnoea) [9]. The widely used but problematic definitions of specific terms are as follows: 'sepsis' is defined as the presence of infection and SIRS; 'severe sepsis' is defined as 'sepsis' with organ dysfunction; and 'septic shock' is defined as 'severe sepsis' with hypotension despite fluid resuscitation [8].

Two recent interventional trials have demonstrated that early recognition and intervention can result in dramatic reductions in acute (28-day) mortality. In March 2001, the first successful, large scale, randomized, double-blind, placebo-controlled trial of a therapeutic intervention in severe sepsis was published [10]. This trial demonstrated that administration of rhAPC to patients with severe sepsis, within 24 hours of diagnosis, reduced mortality by 6.1 % (from 30.8% in the control group to 24.7% in the treatment group). This result indicates that 1 additional life would be saved for every 16 patients treated. APC was approved for clinical use in the USA in November 2001 and is expected to gain approval in the European Union in the coming months. A second major interventional study was also published in November 2001 [11]. In this study, Rivers and colleagues randomized patients with severe sepsis to either standard care or protocolized, goal-directed therapy for the first 6 hours of treatment. They demonstrated a significant reduction in 28-day mortality from 50% in the control group to 33% in the protocol group, which remained significant at 60 days with rates of 57% and 44%, respectively.

Roundtable discussion

The panel were presented with the following questions:

- First, 'Does the panel agree with the findings of a recent meeting of intensive care organizations, which concluded that the SIRS model is too vague?'
- Second, 'Does this panel feel that universal guidelines for recognizing and defining sepsis would help identify patients more effectively?'
- Finally, 'Does this panel feel that the arrival of new sepsis therapies means early identification and early treatment is even more important? Do hospital teams need to be re-educated about identifying and managing sepsis patients?'

Vincent began by asking the panel to define sepsis. Artigas proposed the view that sepsis is a syndrome of systemic inflammation, which occurs in response to infection. He felt that the SIRS criteria were too vague, failed to include vital parameters, failed to consider the site of infection and failed to usefully assess severity of illness. In response, Bakker disagreed that the sepsis syndrome must always be the result of infection as a nonmicrobiological cause of tissue injury could precipitate an identical syndrome of organ dysfunction. He also felt that the SIRS criteria are a useful

concept in the early identification of patients who may have or are developing sepsis, a view supported by Schroeder and Sherry. However, there appeared to be unanimous agreement that the SIRS criteria were overly sensitive and insufficiently specific to be used as diagnostic criteria for sepsis in clinical practice or therapeutic trials.

The panel went on to discuss what elements should be included in the definition of sepsis. Perhaps unsurprisingly, they essentially recreated the 'PIRO' model. Vincent reported that he had participated in the consensus conference held in Washington, DC, USA, in December last year, which had been arranged for the purpose of redefining the sepsis syndrome [12]. He presented to the panel a brief outline of the conference's broader and more detailed, systematic approach to sepsis definition, termed PIRO:

- 1 Predisposing factors: genetic, chronic disease, immunosuppression, etc.
- 2 Infection (and/or nonmicrobial tissue injury?): localized/extended/generalized.
- 3 Response: inflammatory cascades – limited/extensive/very extensive.
- 4 Organ dysfunction: mild/moderate/severe score (Multiple Organ Dysfunction Score [MODS] [13] or Sepsis-related Organ Failure Assessment [SOFA] [14]).

The panel agreed that this approach was a real advance. In particular, this model offers a useful framework from which to educate both nurses and doctors. Vincent and Artigas stressed that the 'Response' and 'Organ dysfunction' may, initially at least, be very subtle, presenting with nothing more than altered mental status or an isolated thrombocytopenia.

The panel also expressed the vital need to be able to identify patients as early as possible, specifically within the first 24 hours of their developing sepsis. Artigas reminded the panel that epidemiological work has suggested that up to 50% of patients with sepsis are outside ICUs, and it is these patients who are at greatest risk of being diagnosed late, with consequently greater organ dysfunction/failure and hence a higher morbidity/mortality. In response, Vincent raised the issue of ICU outreach and questioned the panel members about their institutions and experience of this. It was generally agreed that outreach teams do facilitate earlier recognition of septic patients, which inevitably leads to increased admission pressures on ICUs. Bakker commented that this increase is at least partially offset by a shorter length of ICU stay, as the patients identified by outreach teams tend to be less severely ill on reaching ICU. It also emerged that best practice in this area remains undefined and that there were finite limits to such a service (i.e. intensive care teams cannot look after every patient in a hospital). This is of great concern, as the incidence of sepsis appears set to continue to increase substantially. The panel articulated the reasons for this, identifying an ageing population and advances in – and increased invasiveness of – medical therapies. Coupled

to all this is the public's demand for more intervention; the more done, the greater the risk of developing sepsis. Vincent then raised the complementary solution, that of concentrating educational efforts on health care professionals who work in acute specialties outside intensive care. The panel concurred with Artigas, who stressed the vital liaison between accident and emergency services and ICUs.

The driving force behind early identification is the emergence of the proven benefits of early intervention. Although not discussed, the failure of many interventional studies in septic patients may well be related to the inclusion of some or many subjects with late/established organ dysfunction/failure. Such patients can be considered 'unsalvageable', and hence have negatively biased results. Crucially, the two recent, successful, interventional studies have both specified early interventions [10,11]. Bakker reported that the result of the rhAPC trial has changed the approach of himself and his colleagues. They now feel that there is an efficacious additional therapy that can be given to patients with severe sepsis/septic shock, if identified early enough. Hence, in their ongoing, international, multicentre, open-label study of rhAPC in severe sepsis, Bakker and colleagues actively consider whether each patient fulfils the criteria for entry into the study; in short, there is more of a reason to make an early diagnosis as something positive can be instituted. Artigas concurred but also stressed the proven benefit of early resuscitation as established by Rivers and colleagues [11]. The panel also agreed that a significant proportion of septic patients have failed the inclusion/exclusion criteria of the rhAPC trials. Sherry reported that only 13% of the patients screened at St Thomas' have been entered into the Open Label study. Bakker reported that the inclusion rate was far higher in The Netherlands, and suggested that this may be due to the greater availability of ICU beds, in comparison to the UK. The panel agreed that the efficacy of rhAPC needs to be established in many of these excluded patients. There was also a consensus that such therapies require ICU monitoring to be administered safely.

The panel concurred that studies into the long-term outcome of patients with severe sepsis who survive to hospital discharge were lacking and urgently needed. Artigas commented that from what evidence does exist, it appears that such patients have ongoing morbidity (such as functional limitations), at least for several months, following hospital discharge. This raised the issue of what, if anything, is known about the optimal care of these patients, the impact on their families and who should best care for them. The panel were unanimous that these patients required specialist, proactive care, but felt that this additional work could not be adopted by intensivists.

On a final note, the panel concluded that educating the general public and politicians must be a priority. The ignorance and misunderstanding surrounding sepsis was

profound and threatened to diminish the potential impact of adopting novel therapies/strategies in the treatment of this common and serious syndrome.

Conclusion

The confusing terminology and woolly definitions surrounding sepsis have undeniably had a variety of negative effects. The emerging PIRO model offers the opportunity to reverse this and educate not only health care professionals but also the general public. Development and increasing promotion of educational initiatives such as the Fundamental Critical Care Course (FCCS) [15] and the Acute Life Threatening Emergencies – Recognition and Treatment (ALERT) [16] courses must be encouraged and resourced. The fact that the sepsis syndrome is so common and associated with such a high mortality needs to be communicated far more effectively, not least as a number of effective early treatments/treatment strategies have recently emerged. What remains unclear, at least to some clinicians, is to which patients with sepsis syndrome emergent therapies such as rhAPC should be given. The results of the recent early goal-directed therapy [11] and intensive glycaemic control trials [17] have demonstrated the dramatic effects on mortality that relatively simple interventions can have. However, there remains a strong argument, based both on basic science research [18] and the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study [10], for patients with severe sepsis to receive rhAPC. In view of the fact that it seems unlikely that a further study comparing best simple care with best simple care plus rhAPC will be undertaken, it is impossible to determine the relative and additive value of each of these interventions. The major difference between these interventions is cost with early goal-directed therapy essentially cost neutral, whereas a treatment course of rhAPC will cost approximately US\$6600 per patient [19]. The economic impact of widespread rhAPC use may deter clinicians and/or budget holders from implementing this therapeutic strategy. Biochemical or genetic markers, yet to be defined, may facilitate the identification of patients most likely to benefit, although, notably, using APC levels failed to discriminate in the PROWESS trial. As is all too frequently the case, the questions and aspirations continue to outstrip the answers and resources, and yet signs of positive progress in the management of patients with severe sepsis have finally emerged.

Competing interests

JB received an honoraria and expenses from Eli Lilly and company to attend and report on this roundtable debate.

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Appendix

Chairman: Jean-Louis Vincent, Head of Department of Intensive Care, Erasme Hospital, Brussels, Belgium. Vincent was a participant at the sepsis definition consensus conference (December 2001, Washington, DC, USA), and is one of the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study investigators.

Antonio Artigas, Director of Intensive Care, Sabadell Hospital, Barcelona, Spain.

Jan Bakker, Director of Intensive Care, Isala Klinieken Zwolle, Zwolle, The Netherlands. Bakker is a study investigator in the ongoing international, multicentre, open label study of rhAPC in severe sepsis (phase 3b clinical trial).

Tony Sherry, Senior Research Nurse, Guy's & St Thomas' Trust, London, UK. St Thomas' is the leading UK centre in the ongoing international, multicentre, open-label study of rhAPC in severe sepsis (phase 3b clinical trial).

Michele Schroeder, Senior Research Nurse, Department of Intensive Care, Erasme Hospital, Brussels, Belgium. Schroeder was involved in the PROWESS study.