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CONFERENCE REPORT

An update from the 35th Brussels ISICEM meeting

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Abstract

This report describes the latest news from the yearly Brussels ISICEM meeting held from 16-20 March 2015. Most importantly, opinion leaders concluded that future studies and interpretation of data should be more individualised. Virtually all intervention studies in the recent decennium that were performed in ICU patients show overlapping Kaplan-Meier survival curves. In view of the recent insights derived from omics research we will probably hear more from individualised therapeutic interventions, rather than interventions in more generalised groups. This is also substantiated by an increasing number of closed-loop systems, such as automated weaning from the ventilator, and regulation of glucose levels. New information on specific subjects such as the colloid-crystalloid controversy, end-of-life care, transfusion-related issues, immunonutrition and the early identification of pathogens is briefly discussed.

Introduction

As usual, Professor JL Vincent chaired the opening session of the International Symposium on Intensive Care and Emergency Medicine (ISICEM) on Tuesday morning, welcoming all his friends from around the globe. With almost 9000 attendees, this still remains one of the largest meetings dedicated to emergency and critical care in the world. During that session, several new trials were presented including the PROMISE trial, the ABLE trial, and the paper describing the effects of SIRS in defining severe sepsis. These, and other trials, will be briefly reviewed here. Several new ideas and concepts that were discussed during the meeting will be mentioned in short as well.

Early goal-directed resuscitation in septic shock

Kathy Rowan presented the PROMISE trial on behalf of her co-investigators [1]. They conducted a randomised trial in 1243 patients from 56 ICUs in the UK who received either usual care (n = 620) or early goal-directed therapy (EGDT; n = 623). The primary outcome was 90-day mortality. Hypotension was present in 55% of the patients and average lactate levels were high (7 mmol/l). A similar proportion of patients died in the EGDT group (29.5%) as in the usual care group (29.2%; RR = 1.01 [0.85-1.2]). More fluids, vasoactive drugs, and red cells were infused in the EGDT group, although overall costs in both groups were not different. This study again places some doubts on the value of EGDT in critically ill patients. However, one should remember that the patients in the original Rivers study [2] were enrolled in the emergency room without prior resuscitation. In the PROMISE trial, and also in the other recent PROCESS [3] and ARISE [4] trials focussing on EGDT, standard of care of the patients preceding randomisation was different from the Rivers study. Indeed, usual care groups in all three trials fared much better than in the original studies. In particular, more fluids had been given preceding randomisation, e.g. in the PROMISE trial an average of 2 litres per patient. Indeed, mortality in septic shock has decreased markedly in the last decennium [5]. This change in usual care makes a comparison between the current three EGDT trials and the original Rivers trial almost 15 years ago of little use. A combined analysis of all three trials will appear shortly (PRISM initiative), although a panel of lead investigators disclosed at the meeting that the results will not be different from the results found in the individual trials. So, is EGDT dead? The answer should probably be yes and no. In individual cases, SvO2 monitoring will probably be useful, but aiming therapy at the same non-individualised goals in every septic patient is not useful.

Does age of transfused red blood cells matter?

Paul Hebert presented the results of the ABLE trial [6]. They performed a multicentre, blinded trial in 64 European and

Canadian ICUs and randomised patients to receive fresh RBCs (< 8 days; n = 1211) or to the standard, which was the oldest compatible RBCs in the blood bank (n = 1219). Fresh RBCs had been stored shorter (mean 6.1 days) than the standard RBCs (mean 22 days, p < 0.001). At 90 days, mortality was similar in both groups (37.0% and 35.3% respectively). This result refutes previous findings, albeit in smaller and frequently not randomised study groups. Several factors should be considered when interpreting the results of the ABLE trial. First, the participating centres had already been practising a restricted transfusion policy. This means that ICUs with a more liberal transfusion policy, and inherent larger infusion volumes of RBCs, may differ from the results reported in the ABLE trial. Also, one should keep in mind that only leukocyte-reduced RBCs were used in this study, which could be an important factor due to the in vitro toxic effects of degrading leukocytes. Finally, the study did not address whether very old RBCs, e.g. > 5-6 weeks storage time, are worse than RBCs that have been stored for 2-3 weeks. The conclusion of the authors seems valid in that no clinical improvement was observed when ICU patients received fresh RBCs when compared with older RBCs. There seems to be no need for changing RBC storage policies for ICU patients.

Are the SIRS really dead now?

The systemic inflammatory response syndrome (SIRS) has been addressed frequently in relation to sepsis, for instance in the Sepsis Occurrence in Sepsis (SOAP) study [7]. In that study, 82% of ICU patients without infection proved to have accompanying SIRS according to the established criteria. On the other hand, one-eighth of the patients with infection and organ failure did not demonstrate at least two SIRS criteria resulting in a low sensitivity. Bellomo presented findings in a recent analysis of data from 1,171,797 patients admitted to 172 Australian and New Zealand ICUs in the period between 2000-2013 [8]. They identified patients with infection and organ failure and looked for signs of SIRS. They found that 12.1% of the patients had SIRS-negative sepsis. Both SIRS positive (36.1% to 18.3%) and SIRS negative sepsis patients (22.7% to 9.3%) demonstrated a significant reduction in mortality in the study period. In the adjusted analysis that the authors performed, mortality proved to be linearly related to each additional SIRS criterion that was present. The authors concluded that the use of two SIRS criteria to define severe sepsis excluded one-eighth of the patients with infection, organ failure and substantial mortality. They challenge the current consensus cut-off and propose that these definitions should be reconsidered.

Immunonutrition and pharmaconutrition

In animal studies it has been shown that reactive oxygen species cause damage to cells that can ultimately lead to adverse outcomes in terms of morbidity and mortality. In healthy humans, preventive supplementation of antioxidants to counteract the effects of these reactive oxygen species has been shown to lead to a higher mortality. However, in critically ill patients there is a high burden of oxidative stress so there may be a rationale for antioxidant use in the ICU. Unfortunately, almost every study performed in this field has used a combination of antioxidants in various patient groups; single nutrient studies are hard to find. The latest trials were presented by Van Zanten et al. with specific attention to the Metaplus trial.[9] The authors concluded that there was no beneficial effect of using an enteral high-protein 'immune-modulating' formula in terms of length of stay, ventilator-free days, nosocomial infections or mortality, and it may even cause harm (increased adjusted mortality at 6 months).

With regard to the use of fish oil, the publications by Edmunds et al. [10] and Grau et al. [11] were presented. In both studies a significant reduction in infections was shown, but no positive effects on other outcome measurements. The latest meta-analysis by Manzanares [12], including these studies, showed a potential benefit of nutrition containing fish oil. However, because of the paucity of data it was concluded that there is inadequate evidence to recommend the routine use of fish oil. In addition, it was shown that in all studies with a positive effect of fish oil the control groups were fed with a nutritional formula containing high levels of omega-6 fatty acids. This bears the question whether the positive effects in the included studies could be attributed to using fish oil or that the control groups had worse outcomes because of the harmful effects of high doses of omega-6 fatty acids. In conclusion, as was published recently by a group of experts as part of an overview of nutritional support [13], current evidence does not support the routine use of pharmaconutrition or immunonutrition in a general ICU population.

Figure 1. Carnivorous pitcher plant *Nepenthes*.

What can be learnt from nature?

Researchers from the Wyss Institute for Biologically Inspired Engineering at Harvard University recently developed an artificial substance composed of liquid perfluorocarbons. Based on the fact that current anticoagulant strategies cannot fully prevent the formation of clots when using artificial devices (central venous catheters and haemodialysis filters for example), this research group looked at the Slippery, Liquid-Infused, Porous Surface (SLIPS) approach for prevention of thrombosis. Inspiration came from the carnivorous pitcher plant Nepenthes, which uses a layer of water on the inside of its leaves to create a slippery surface to which insects cannot attach (*figure 1*).

The Wyss Institute copied this plant's method by coating a range of material surfaces with a flexible perfluorocarbon layer and coating this layer with a mobile layer of perfluorodecalin, which has FDA approval for use as a blood substitute. This antithrombogenic dual layer technique is referred to as TLP. TLP surfaces effectively repel whole blood and resist adhesion of blood components and bacteria. The researchers demonstrated, in a pig model without the use of anticoagulants, that TLP coating of the interiors of tubes and catheters led to a normal blood flow without clotting for eight hours [14]. Several video clips were shown with droplets of blood 'rolling' on TLP-coated surfaces without leaving a smear of blood. The most convincing clip, however, was the one showing that even a gecko, known for its sticky footpads, could not get a grip on a TLP-coated surface. In conclusion, TLP coating of artificial devices seems a promising technique for reducing thrombosis and anticoagulant use in a wide range of clinical settings.

Haemoglobin threshold for transfusion in septic shock

In 1999, the Canadian Transfusion Requirements in Critical Care (TRICC) trial [15] indicated that a lower transfusion trigger of 7 g/dl was safe and, in certain subgroups, even preferential to a more liberal transfusion strategy. The problem with this trial was that it was performed in a broad ICU population, with relatively few septic patients. On the other hand, the surviving sepsis campaign [16] advocates a haematocrit of higher than 30, while experimental data [17] showed better recruitment of the microcirculation with higher haemoglobin concentrations.

To shed more light on this question, Anders Perner and colleagues performed the multicentre Transfusion Requirements In Septic Shock (TRISS) trial [18]. Patients admitted to the ICU with septic shock and a haemoglobin level of 7 g/dl or less were randomised into a lower threshold (7 g/dl) or higher threshold (9 g/dl) group. The lower threshold group received 1 unit of blood, compared with 4 units in the high threshold group. There was no difference in 90-day mortality between the two groups (primary outcome), nor any difference in use of life support, the incidence of ischaemic events, or adverse effects between the groups (secondary outcomes). It is worth noting that patients with acute coronary syndrome and active life-threatening bleeding were excluded from the trial.

Personalised medicine is the future

Hector Wong explored the future of personalised medicine with a look at the pathways being forged in this direction in sepsis research. The aim is to develop new tools at the bedside and optimise tailored therapies. In particular, analysis of gene variants and the genome with differences in protein synthesis and clinical phenotypes was discussed, e.g. procoagulant response or anti-inflammatory response to a certain trigger. This may mean that many, if not all, trials with pharmaceutical compounds that have been performed thus far in certain disease states in the critically ill have to be reviewed and sometimes redone in specific subgroups who may theoretically benefit from this more individualised approach. Much research in the coming years will focus on genomics and proteomics in this respect.

In line with this thought, Van der Poll showed why sepsis and septic shock are very heterogeneous syndromes [19, 20]. The host response to bacterial infection may vary from a balanced response with full recovery on the one hand, to an unbalanced response with early death due to hyperinflammation on the other hand, or even be related to late death due to immune suppression [21]. There is an urgent need for biomarkers that reflect the predominant type of the host response in individual patients. Immunotherapy or immune modulation in sepsis may be feasible, especially if the activity or expression of the pathway that is targeted can be measured by a simple bedside test which can also assist in monitoring the pathway-specific effect of the intervention.

Integrating palliative care in the ICU

Palliative care in critical care patients has gained attention during the past decades. How far have we come and what must still be done to meet the values and goals of patients with serious illness? Curtis recently published on the relationship between advanced palliative planning and ICU utilisation as well as the perception of quality of dying from the perspectives of both families and clinicians [22]. With this study the authors aimed to increase the awareness of the importance of palliative care in the ICU. Palliative care and end-of-life care should not be equated because palliative care is defined as care for patients with a serious illness that focuses on patient's values and maximising quality of life. Palliative care can explicitly be used alongside curative therapies or in case the critical illness turns out to be life limiting. In contrast, end-of-life care is only considered when a patient's death is imminent. Since each patient and family has different needs, the goal is to identify those individual needs and to try and fulfil them. This means

that it is crucial that intensivists should spend time to talk with patients and their families to provide appropriate care in the critical care setting that matches the patient's values and goals.

A new era for research on HES and crystalloid solutions

The rise and fall of the administration of hydroxyethyl starch (HES) colloidal solutions in the recent years has launched a lot of new research on an old theme. HES solutions were an important part of fluid therapy in septic shock but due to the negative effects on organ function the use of HES was abandoned. Crystalloid fluids regained their position in fluid therapy in sepsis. However, attention had already been focused on the possible negative effects of physiological solutions. In particular, hyperchloraemia was found to contribute to mortality, partly because of negative effects on renal function. Balanced crystalloid solutions were introduced and a few studies showed even a small survival benefit [23]. Previously widely accepted use of crystalloid fluids was converted to deliberate use as is usual for new pharmaceuticals. The information about the clinical pharmacology of crystalloid fluids is scarce in medical literature. The mechanism of action, the distribution throughout the compartments and the elimination has regained a lot of research interest [23]. In coming years, the results of multicentre studies on the effects of crystalloid and balanced substitution fluids, especially in the treatment of severe sepsis and septic shock, were announced.

HES solutions were also used for their supposed colloid osmotic effect in case of fluid overload. New research has recently focused on this aspect. Some preliminary studies were presented demonstrating the use of HES in combination with furosemide in patients with an access of interstitial fluid. Especially the use of this strategy in patients treated with haemofiltration is interesting. A 'staircase' approach was suggested. In this presentation HES was used in a build-up scheme and showed no deleterious effect on renal function. A difference in the pathophysiology of the underlying disease, sepsis or intravascular fluid shortage seemed to be a possible explanation.

Another interesting session about hot topics 35 years ago showed that many points of view (once even state of the art) had not withstood the test of time but did initiate a lot of research leading to interesting new concepts that are now guiding us in the understanding of our critically ill patients. One of these subjects is, not surprisingly, the renewed interest in crystalloids.

Early detection tools in infection

One of the cornerstones of the treatment in sepsis involves the empiric start of broad-spectrum antibiotics, preferably as soon as possible after obtaining cultures. Nevertheless, only 10% of blood cultures will prove to be positive. In addition, these results will frequently require cultures for at least 48 hours. Recently, several companies have embarked upon the development of alternatives to get faster and reliable results on the pathogens involved in critical illness. Using smart PCR techniques, the time between obtaining a sample and diagnosis will decrease from 48 to less than 6 hours in the next years. Growing numbers of genomic libraries of gram positive and negative bacteria, but also yeasts and other microorganisms, will improve reliability and even be able to predict potential resistance to specific antibiotics. This will have a serious impact on the way physicians treat critically ill patients.

Preliminary results from the recently finished RADICAL study were presented [24]. In that multicentre observational study, results from direct blood specimen testing using PCR coupled with electrospray ionisation mass spectrometry (PCR/ESI-MS) were compared with standard microbiology in critically ill patients. Eight ICUs in six European countries participated in that study. Patients could be included if they had a suspected infection plus ≥ 2 new-onset SIRS criteria. PCR/ESI-MS was reliably able to identify the infective micro-organism. Moreover, an independent expert panel would have considered a different course of antibiotic regimen in 57% of the cases when PCR/ESI-MS was positive, 41% of which would have resulted in altered, instituted, or ceased antibiotic therapy, earlier.

Currently, prospective studies are in progress trying to show that these new techniques can indeed be used safely in clinical practice and will potentially be cost-effective, reduce the induction of resistance, and reduce mortality.

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