Commentary
Recently published papers: Curing, caring and follow-up
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Ups and downs in the fight against sepsis

Sepsis is a major cause of critical illness, with a mortality rate in the range of 30–50%. Two landmark papers have been published in the past 18 months that have significantly furthered our ability to manage sepsis and to reduce the high mortality rate associated with it [1,2]. The future seemed brighter.

Following the success of the activated protein C trial in 2001 [1], interest in anticoagulant therapy for severe sepsis was heightened. A systemic imbalance between procoagulant and anticoagulant pathways exists in severe sepsis, leading to thrombus formation in the microvasculature and to subsequent end-organ injury. Endothelial injury occurring in severe sepsis is thought to be a trigger for this process, initiating the clotting cascade via the transmembrane receptor, known as tissue factor, and its interaction with factor VII. Inhibition of this interaction would block the coagulation pathway at its earliest point.

With this concept in mind, July witnessed the publication of a large multicentre phase 3 randomised, double-blind, placebo-controlled, clinical trial investigating the efficacy and safety of recombinant tissue factor pathway inhibitor (TFPI) in severe sepsis [3]. Two subgroups of patients were randomised to either a 96-hour infusion of active drug or to placebo: a high International Normalised Ratio (INR) group (INR ≥1.2, 1754 patients), and a low INR group (INR ≤1.2, 201 patients). The study failed to demonstrate any survival benefit in the treatment groups, although there was a trend to improve survival in the small low INR subgroup. Furthermore, the study showed that TFPI administration was associated with an increased risk of bleeding, predominantly from gastrointestinal and respiratory tracts.

One of the more striking peculiarities of this study is the reversal in fortunes of the treatment and placebo groups halfway through the enrollment period. At a planned interim analysis the mortality rates favoured the TFPI group (29.1% versus 38.9%). In the latter portion of the study, however, an increase in the TFPI group mortality and a decrease in the placebo group mortality totally reversed this effect. No satisfactory explanation for this phenomenon has been found despite exhaustive efforts. If the study had been stopped following the interim analysis I could now be writing a very different report.

To confuse matters further, as in the antithrombin III trial [4], heparin administration, which was not part of the trial protocol, appears to have confounded results. Heparin binds to TFPI, thereby interfering with its biological action and masking any beneficial effect. Stratification of mortality rates for those who did receive heparin and for those who did not receive heparin appears to support this concept. In the placebo groups, however, patients receiving heparin suffered a lower mortality than those who did not. As pointed out in Angus and Crowther's typically erudite and enlightening accompanying editorial, this data must be treated with caution because heparin administration was not randomised [5]. But surely the time is nigh for a detailed study of heparin? Within the editorial, Angus and Crowther also challenge the decision to predominantly target patients with elevated INRs, this decision having been based upon analysis of a prior phase 2 trial. They emphasise the difficulties and dangers of using small phase 2 trials as the basis for critical design decisions of much larger phase 3 trials.

End-of-life care

From strategies aimed at saving lives we turn to those aimed at assisting patients through the dying process. The Ethicus study [6] prospectively collected data on end-of-life practices for consecutive patients admitted to 37 European intensive care units (ICUs) over an 18-month period. In particular, the

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HS = hypertonic saline; HSD = hypertonic saline and dextran; ICU = intensive care unit; IH = induced hypothermia; INR = International Normalised Ratio; QOL = quality of life; TFPI = tissue factor pathway inhibitor.

study aimed to determine the incidence and variation in the nature of end-of-life-practices, and to describe associated variables. The study prospectively defined five mutually exclusive patient categories:

1   Patients having undergone unsuccessful cardiopulmonary resuscitation.
2   Patients diagnosed with brain stem death.
3   Withholding life-sustaining treatment.
4   Withdrawing life-sustaining treatment.
5   Active shortening of the dying process.

Out of the 31,417 patients admitted to the participating ICUs during the study period, 4248 (13.5%) died or had their treatment limited in some way. The mean age of the study population was only 63 years. A summary of the main results as a percentage of the study population is presented in Table 1.

The Ethicus study demonstrates what many of us already know. Limitation of treatment in the critically ill is widely practiced, although active shortening of the dying process is rare. The majority of the reported active shortening of the dying process practices came from a handful of centres. Withholding usually preceded withdrawing, which preceded active measures. Regional differences were shown, with southern European countries practicing cardiopulmonary resuscitation more and northern European countries withholding and withdrawing more. Unsurprisingly, clinical factors such as age, diagnosis and time on the ICU were variables associated with the likelihood of treatment limitation. Surprisingly, treatment limitation was more probable if the physician was Catholic or Protestant rather than Greek Orthodox, Jewish or Muslim.

This intriguing study highlights the variability in end-of-life practices across Europe, and the many complex factors, both objective and subjective, clinical, geographical, cultural and religious, which contribute to the decision-making process. For an area that many find one of the most demanding aspect of critical care medicine the lack of consensus is disturbing, but this trial is a significant step in the right direction.

After the ICU

Surviving a period of critical illness may seem to be the end that justifies the means. Indeed, improvement in survival is

often the yardstick by which we judge our interventions. In recent years, however, a growing body of evidence suggests that for patients the story does not end at the point of leaving the ICU alive. The quality of life (QOL) may be seriously impaired in significant numbers of patients. But how we identify these patients and the factors that influence to what extent and for how long their lives are affected by critical illness is unknown. Understanding these parameters would surely alter the clinical decision-making processes and enable us to better inform patients and relatives regarding critical illness. Two prospective observational studies published in *Intensive Care Medicine*, one Belgian and the other Finnish, go some way to achieving this [7,8].

The first of these studies investigates the QOL in ICU survivors 18 months post discharge, and the second compares the QOL 1 year and 6 years post ICU discharge. In the Belgian study, 38% of those who completed the questionnaire had a worse QOL than prior to admission, although only 8.3% were severely impaired [7]. Rather than suffering physical disability, pain, discomfort, anxiety and depression were the most reported QOL issues. Severity of illness (Acute Physiology and Chronic Health Evaluation II) and ICU readmission were associated with increased post ICU mortality, whereas age was not. Sixty-two per cent of respondents had returned to work at 18 months post discharge, a result consistent with other studies.

The study from Finland compliments the Belgium study. Nine per cent of patients at 6 years post ICU discharge considered their health status to be very poor [8]. As might be expected, psychological well-being had improved when compared with 1 year post ICU discharge whereas physical functioning had deteriorated, suggesting the existence of an evolutionary process of post ICU morbidity. This in turn perhaps points to the kind of therapeutic support patients may require. The Finnish authors suggest strategies to reduce early psychological morbidity such as keeping patient diaries by staff and relatives to be used later as a means of reducing patient amnesia, a well-recognised cause of mental distress.

These two studies make it difficult to ignore the need for comprehensive ICU follow-up and for a better understanding of the long-term natural history of critical illness.

Table 1

Frequency of patient end-of-life categories

	Cardiopulmonary resuscitation	Brain death	Withholding	Withdrawing	Active shortening of the dying process
Patients (%)	19.6	7.8	37.5	32.9	2.2
Mortality (%)	100	100	89	99	100

Other papers of interest in brief

Chiara and colleagues report on the results of a laboratory trial of resuscitation from haemorrhagic shock comparing normal saline, dextran, hypertonic saline (HS), and a mixture of hypertonic saline and dextran (HSD) in a porcine model [9]. Measured parameters were the restoration of mean arterial pressure, the aortic, mesenteric and renal blood flow, the cardiac output, and the oxygen consumption and delivery indices. Their main findings were:

- HS allows complete haemodynamic resuscitation using smaller volumes.
- Resuscitation is sustained longer using HSD.
- Recovery of renal and mesenteric blood is rapid and with no concomitant pulmonary hypertension using HSD.
- HSD maintains its haemodynamic effects longest post cessation of fluid administration.
- Sodium concentration and osmolality were not problematic using HS or HSD.

The theoretical advantages of HS and HSD solutions have been recognised for some time, but we await a definitive clinical trial.

I recommend two review articles in the July issues of *Chest* and *Critical Care Medicine* [10,11]. Kreider and Lipson review the evidence for the much-loved practice of bronchoscopy in critical care patients with mucus plugging/atelectasis. In essence, they conclude that bronchoscopy is of use in the management of atelectasis, particularly lobar, but there is no evidence to suggest it is superior to less invasive techniques such as good physiotherapy [10]. Also, bronchoscopy is associated with potentially harmful physiological side effects such as hypoxaemia, elevated airway pressures and raised intracranial pressure.

Finally, in a review of the use of induced hypothermia (IH) in critical care medicine, the physiological effects of IH and its clinical applications are discussed [11]. Following the excitement generated by two papers reporting the successful use of IH in the management of prehospital cardiac arrest [12,13], this article represents a well-balanced discussion of the evidence for and against IH and the practical issues of its implementation.

Competing interests

None declared.

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