Evidence based practice in intensive care—light on the horizon?

The practice of intensive care medicine, although now on a much firmer footing, is nevertheless an emerging speciality. Foundations were laid in the 1950s, and although other countries were ahead, this at present multidisciplinary practice has only recently gained speciality recognition within the UK from the Specialist Training Authority (STA). It would have been expected that such a new speciality would have been entirely governed along the modern evidence based practice system. This, however, is not the case. It is perhaps the perception from those not working in intensive care that those practitioners who do are reluctant to be guided along evidence based medicine and critical care medicine is consequently lagging behind other areas of medical practice.

A recent Editorial in this journal on parenteral and immunonutrition along with the subsequent letters of rebuttal and a reply from the original authors illustrates the concerns well. The conclusion is that ‘many intensivists have a voracious appetite for novel unproven therapies’. To an extent this perception is correct. However, at last, things are about to change.

Undertaking research in critically ill patients is notoriously difficult and, therefore, much of the original and groundbreaking work in the speciality has involved animal models. These have been useful to an extent but as much of the practice of intensive care involves multiple disease processes, animal models cannot precisely mimic the human situation. Mice are not men. Nowhere is this more apparent than in the area of sepsis, which is still a major contributor to mortality on the intensive care unit. Another difficulty, which has perhaps delayed the accumulation of evidence on which to base our practice, is the lack of a single disease entity to study. For example, cardiology is often cited as a good example of a speciality that practices evidence based medicine. However, many of the trials in this area concentrate on very specific conditions and most are funded by the pharmaceutical companies who look to the large potential market to support the costs of the research. The average intensive care unit has a wide range of conditions and patients with varying underlying abnormalities of baseline physiological reserve. It is, therefore, unlikely that a single intervention will influence the outcome of such a diverse population.

Further support for the suggestion that intensive care practitioners are reluctant to wholeheartedly embrace evidence based practice is the widespread hue and cry that has ensued as a result of the recent papers addressing the use of albumin and pulmonary artery catheters. These papers are the results of meta-analyses of a large collection of small studies of varying quality. Although there has been much criticism of both papers, the use of albumin has declined appreciably and more workers are questioning the routine use of pulmonary artery catheters. So perhaps intensivists are willing to alter practice—but not to admit to it.

Of more significance, however, is the very recent appearance of five separate studies all of which will have an impact on intensive care practice. All five reports are the result of large, well-conducted randomized studies involving intensive care patients and all have shown a significant reduction in mortality. Although much of this work is currently only available in abstract format and so has not been through the peer review process, all will result in changes of practice. Perhaps at last there is a light on the horizon for evidence based practice in intensive care.

Mechanical ventilation

The traditional approach to mechanical ventilation has been to use tidal volumes considerably in excess of normal—usually around 10–15 ml kg\(^{-1}\). This has been necessary to correct hypoxia and hypercarbia and prevent atelectasis. However, there has been increasing evidence of the damaging effects of such ventilation patterns from a variety of animal studies. Large tidal volumes in animals are associated with disruption of pulmonary capillary endothelium and alveolar epithelium, lung inflammation, and the systemic release of inflammatory mediators. This latter effect may then result in injury to other organs. Uncontrolled studies in patients with acute lung injury have suggested that the use of lower tidal volumes may be associated with a better outcome. Four small, randomized trials showed conflicting results—there was, therefore, a state of equipoise and clearly a need for a large, well-conducted, randomized trial. Such a trial was designed and conducted and was stopped after an interim analysis because of overwhelming benefit. In this study, 861 patients were...
randomized to either a ventilatory strategy aimed at preventing lung damage or to ventilation at traditional higher tidal volumes. The mortality rate was 39.8% in the traditional ventilation group and 31.0% in the lung protection group (P=0.007). The lung protection ventilator strategy used was: a tidal volume of 6 ml kg\(^{-1}\) of predicted body weight, reduced by 1 ml kg\(^{-1}\) if necessary to maintain plateau pressure <30 cm H\(_2\)O; ventilator rate set to 6–35 min\(^{-1}\) to achieve a pH goal of 7.3–7.45; and PEEP varied according to inspired oxygen tension using a standard table. This ventilator strategy will now become the gold standard against which all others will be compared and should form the basis for good practice.

**Steroids in sepsis**

A previous study of high dose steroids concluded that steroids had no place in the management of patients with sepsis as outcome was significantly worse.\(^9\) However, there have been recent reports of the value of lower dose steroids to correct refractory hypotension.\(^10\) There is now a preliminary report of the value of low dose steroids in patients with sepsis, which is the result of a large, randomized controlled trial conducted in France.\(^11\) In this study, 299 patients in septic shock were studied and 229 were found not to respond to a short Synacthen test. Patients were randomized to receive either steroid treatment with hydrocortisone 50 mg intravenously 6 hourly and fludrocortisone 50 mg once per day orally or placebo, for 7 days. There was a 30% decrease in the risk of death following the use of steroids in these patients, with most of this effect being a result of improvements in the non-responder group. Clearly this is an early report of an interesting study, which could well change the standard management of septic shock.

**Anti-TNF in sepsis**

A monoclonal antibody to tumour necrosis factor-\(\alpha\) (TNF-\(\alpha\)), one of the early mediators in sepsis, was evaluated a few years ago in three large multinational studies.\(^12\)-\(^14\) Although initially very promising in animal studies and the early studies in humans, results from three large, randomized studies of the same monoclonal antibody which enrolled a total of 3537 patients with severe sepsis failed to show any statistically significant benefit. Animal models have now allowed us to appreciate the multitude of regulatory processes that interact during sepsis, and also the redundancy involved in this regulation. A lack of appreciation of these facts has probably resulted in the failure of many new treatments in the septic patient. It is, therefore, interesting that an early report of a new study has shown a significant, although small, benefit of a new anti-TNF-\(\alpha\) molecule.\(^15\) A total of 2634 patients with sepsis were enrolled into a placebo controlled randomized trial which showed a decrease in mortality from 35.9 to 32.3% (P=0.049). The mortality difference is small but the study does at least demonstrate that it is possible to conduct well-designed trials in such a heterogeneous population of patients and demonstrate a statistically significant difference in outcome.

**Activated protein C**

A number of small studies and case reports have suggested a possible beneficial effect of protein C in patients with severe sepsis. The rationale for using protein C originated because of the coagulopathy often seen in sepsis and the quite significant risk of tissue loss associated with intravascular thrombosis particularly in meningococcal sepsis. Activated protein C has both anti-thrombotic and pro-fibrinolytic activity. Phase II studies confirmed the efficacy of protein C in sepsis with regard to the coagulopathy but were not powered to demonstrate a conclusive mortality benefit. A phase III study of recombinant human activated protein C was halted at an interim analysis and the initial results are currently published only in abstract form.\(^16\) A total of 1690 patients with severe sepsis was enrolled into the study before it was halted and mortality was decreased from 30.83 to 24.72% in the treatment group (P=0.0054). The mortality rate in the placebo group of patients is low but not that different to that found in the anti-TNF study. Hopefully, further data analysis of these results will provide more useful information. It is also possible that activated protein C had this beneficial effect via an anti-inflammatory action rather than any effect on the clotting system. It is again clear that a well-conducted trial is possible in the intensive care population. It is possible that this is another approach to the management of patients with sepsis that will change the practice of those working on intensive care.

**Renal dose dopamine**

Low dose dopamine is commonly used to increase renal blood flow, induce natriuresis and diuresis, and also theoretically to prevent patients developing renal failure by offering renal protection. Although there have been many small trials demonstrating a lack of renal protection, practitioners have continued to use the drug for this purpose and there were emerging worries about the harmful effect of dopamine on pituitary function. A randomized study which enrolled 328 patients has recently been published which should hopefully change current practice.\(^17\) In this study, peak creatinine concentrations and the requirement for renal replacement therapy were identical in those receiving dopamine 2 \(\mu\)g kg\(^{-1}\) min\(^{-1}\) to those receiving placebo. The accompanying editorial asked us to ‘stop hedging and accept that there is no justification for using renal dose dopamine for renal protection’.\(^18\)

Evidence based medicine should be considered more a way of life than simply a way of dictating how patients and clinical problems are managed. It is a process of self-directed learning that should continue throughout our
working practice. There are five components to evidence based medicine:
1. identify relevant questions;
2. track down the best evidence to answer these questions;
3. critically appraise the evidence;
4. apply the results of the appraisal to clinical practice; and
5. evaluate performance following the change in practice.

There are many relevant questions that surround the practice of intensive care medicine. However, the best evidence with which to answer these questions has often been missing. Well designed and carefully conducted controlled, randomized and double blind studies, which evidence based medicine and it is these which have been lacking.

All five examples demonstrate that it is possible to conduct conclusive studies in the critically ill, despite the wide mix of underlying pathology and baseline physiological reserve. Intensivists are capable of asking the right questions and undertaking the research to a strictly agreed protocol—both essential parts of evidence based practice. The next step is how to introduce the change in practice on the basis of the studies undertaken. It is this last crucial step that is the hardest. Moreover, how best to implement change, has received little attention in the past. This is the issue for the next few years.

Although we all know that renal dose dopamine does not protect the kidney it is nice to see the urine flowing. But we have to believe what we read following a critical appraisal rather than seeing with our own eyes the volume of liquid in the urine bag. However, we are not alone—some of our surgical colleagues still ask ‘have you started the dopamine?’

N. R. Webster†
Institute of Medical Sciences
Foresterhill
Aberdeen AB25 2ZD
UK

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Note added in proof

†Conflict of interest: Professor N. R. Webster is a member of the Zovant Advisory Board of Eli Lilly UK.