

# The Surviving Sepsis guidelines: evidence-based ... or evidence-biased?

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While the Surviving Sepsis Campaign<sup>1</sup> is certainly worthy in its attempt to introduce evidence-based medicine into the management of sepsis, the resulting document is sufficiently flawed to engender genuine concern. Although I have no issues with many of the recommendations — indeed, many match my own current practice — there are enough instances of evidence-biased mishmash to prevent me providing a ringing endorsement of the document as a whole. Space limitations restrict me to simply categorising the problems, illustrating with examples, and summarising my concerns.

## How strong is the evidence?

Of the 50 plus recommendations in the Surviving Sepsis Campaign guidelines, more than half were classified as “grade E” — ie, based on non-randomised historical controls, case studies, uncontrolled studies and expert opinion. Hardly overwhelming and reassuring. Only five recommendations warranted a grade A classification (avoid supranormalising oxygen delivery; avoid high-dose corticosteroids, use a weaning protocol and spontaneous breathing trials, and give prophylaxis against deep venous thrombosis [DVT] and stress ulcers). However, apart from the corticosteroid studies, none of the studies were confined to sepsis, and their results were usually extrapolated from general intensive-care populations. Is this appropriate? As an example, the SAFE (Saline versus Albumin Fluid Evaluation) study showed no overall benefit from albumin compared with saline in critically ill patients, but a near-statistical benefit in the subset with sepsis.<sup>2</sup>

Secondly, two of these five grade A recommendations were not supported by “at least two level I investigations” as defined — ie, large randomised trials with clear-cut results. Take, for example, DVT prophylaxis with heparin, where three trials were cited as supportive evidence.<sup>3-5</sup> One 1982 study did randomise 119 ICU patients,<sup>3</sup> but another (published a year earlier) comprised 100 general-ward patients with heart failure and chest infection.<sup>4</sup> In both, DVT was diagnosed by <sup>125</sup>I fibrinogen scanning, but what mention was made of clinical outcomes in these historical studies? The third study — the most recent (1999) and by far the largest ( $n = 1102$ ) — recruited “very few” patients from ICUs.<sup>5</sup> Indeed, endotracheal intubation, platelet count

$< 100 \times 10^9/L$  and international normalised ratio (INR)  $> 1.2$  were exclusion criteria! However, to quote the guidelines:

Although no study has been performed specifically in patients with severe sepsis, large trials confirming the benefit of DVT prophylaxis in general Intensive Care Unit populations have included significant numbers of septic patients.<sup>1</sup>

Hmmm. Not by my reading of their cited references.

## Is there bias?

For a document that purported to reflect published evidence, there were some startling omissions. For example, more randomised studies in infection and sepsis prophylaxis have been performed on selective gut decontamination than any other putative treatment, yet this did not even warrant a mention! Nor did the guidelines cover other modalities that have also been subjected to randomised trials, such as plasmapheresis. Does this reflect the antipathy of the authors to these particular treatments? If we are being asked to base our management on the evidence, shouldn't all relevant randomised controlled trial data be presented?

## Dodgy advice?

The guidelines' advice for “fluid challenge” (Grade E recommendation) is to give 500–1000 mL crystalloid or 300–500 mL colloid over 30 minutes, and to repeat “based on response until tissue hypoperfusion is relieved or there is evidence of intolerance of fluid resuscitation, ie volume overload”. So we should stop when pulmonary oedema comes up the endotracheal tube? Would anyone argue that iatrogenic fluid overload is safe? Would it be more sensible to give guidelines as to when to use more sophisticated haemodynamic monitoring to better titrate fluid input, rather than to react post-drowning?

## Over-interpretation, under-powering?

The recommendation for aggressive initial resuscitation was classed as grade B, based on the study of Rivers et al in emergency-room patients with sepsis.<sup>6</sup> Once a central venous pressure of 8–12 mmHg has been attained, we are

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encouraged (a further grade B recommendation) to use packed red blood cells to raise the haematocrit above 30% and/or to give dobutamine to a maximum dose of 20 µg/kg/min to achieve a central or mixed venous saturation of 70%. However, in the Rivers et al study of 263 patients, a mere 18 (14%) of the 130 protocol patients received dobutamine in the first 6 hours, and the outcomes of this patient subset are not stated. For all we know, they may even have fared particularly badly. A clear example of flimsy evidence!

### Bundles of joy?

In cahoots with the Institute of Healthcare Improvement (IHI), a “not-for-profit organization driving the improvement of health by advancing the quality and value of health care”, the Surviving Sepsis Campaign is offering us Severe Sepsis Bundles to implement, which “will substantially reduce mortality due to severe sepsis”.<sup>7</sup> The IHI website continues:

A “bundle” is a group of interventions related to a disease process that, when executed together, result in better outcomes than when implemented individually. The individual bundle elements are built on upon [sic] evidence-based practices. The science behind the elements of a bundle is so well-established that their implementation should be considered a generally accepted practice.<sup>7</sup>

How's that for a collection of “datapenic” and totally unsubstantiated statements?

The dangers of this evangelical zeal are already becoming apparent — in the United States there is concern about financial threats by medical insurance companies and medicolegal actions against hospitals that fail to implement this practice based on “well-established science”. Sadly, in the United Kingdom, some critical care networks have jumped on a similar bandwagon and are trying to railroad this practice through without, in my opinion, sufficient cognisance of the flawed literature. We are all too well aware that today's truth is tomorrow's chip paper. Whatever happened to Centoxin, supranormal oxygen delivery, and the other fads that were so strongly portrayed in their heyday as “fact”?

We need to know how many parts of the bundles are actually ineffective, thus creating unnecessary extra work. Are any perhaps harmful, as many have not been submitted to adequately powered randomised controlled trials? Why are they not being formally tested and validated before

implementation? The sum of the parts may certainly not exceed the individual components. Are we completely sure that giving, for instance, activated protein C and corticosteroids is synergistic, not antagonistic? I fear that homogenising practice will discourage rational deviation and innovation. By standardising care, it may indeed drag the “bad” ICUs up but, potentially, high performance units could suffer. Yet, we are warned that:

Hospitals should use the bundles to create customized protocols and pathways that will function well within their institutions. However, *all of the elements in the bundles must be incorporated in those protocols*. Addition of other strategies not found in the bundles is not recommended ... if not all of the elements of the bundles are incorporated into your customized protocol, your performance on the measures will suffer.<sup>7</sup>

We need conclusive proof that this standard of care is actually better. Perhaps we should be investigating the “good” and “bad” ICUs, to discern differences in practice and to take a research-based lead from them?

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