The Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008 and the Australian and New Zealand Intensive Care Society (ANZICS)

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on behalf of the ANZICS Board and
the ANZICS Clinical Trials Group Executive Committee

The Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008[1,2] is a comprehensive and ambitious attempt to define and implement best practice internationally for the management of critically ill patients with severe sepsis and septic shock. Many treatment recommendations are logical, appropriate, and based on careful examination and grading of the relevant literature. Promulgation of evidence-based guidelines in general is an advance welcomed by clinicians. Furthermore, the comprehensive nature of these Guidelines, and the substantial international reputations of the many authors, makes it likely that they will become a practice standard for the multifactorial management of severe sepsis and septic shock, and a benchmark against which the performance of individuals and groups may in future be measured.

Treatment guidelines are inevitably constrained by the quality of the current evidence, and several important elements of the 2008 Guidelines do not have definitive support from the available published research. Some do not reflect current practice by Australian and New Zealand intensive care physicians. Several guidelines are supported by only a single-centre trial, others by a subgroup analysis from a larger trial. Clearly, "best evidence" is a dynamic construct, and some of the less well supported 2008 Guidelines may in time become acceptable to Australian and New Zealand intensivists, as more trials are completed and published.

The Australian and New Zealand Intensive Care Society (ANZICS) has therefore reluctantly concluded that it would not be appropriate to sponsor the entire package of the 2008 Guidelines, because some components do not reflect current practice in Australia and New Zealand, and some have not been proven superior to current practice binationally. Some examples highlight the considerations behind this decision.

Early goal-directed resuscitation of the septic patient during the first 6 hours after recognition. (Grade 1C.)
The grade of this recommendation, 1C, is defined by the Guidelines as a "strong" recommendation with a "low" evidence quality. It has prominence as the first key recommendation in the Guidelines. However, the package of intensive care described as early goal-directed resuscitation (or therapy — EGDT) is based on a single-centre randomised trial conducted in the United States,[3] and is controversial. In 2007, in preparation for an Australian randomised trial of EGDT, the investigators assessed contemporary Australian and New Zealand practice in relation to EGDT in an observational study of 30 sites, and found that none practised the EGDT package of care as described by Rivers et al.[3] The National Health and Medical Research Council (NHMRC) subsequently funded a multicentre randomised trial (Australian Resuscitation in Sepsis Evaluation — ARISE) to determine the relevance of EGDT in a multicentre Australian setting. In the United States, the National Institutes of Health are supporting a multicentre American trial of EGDT. Both large studies are underway because clinicians in both countries were uncertain about the generalisability of EGDT beyond the single centre. Equipoise among emergency and intensive care physicians enabled EGDT and current-practice treatment groups to be included in both these studies. When these multicentre trials are complete, there may be sufficient evidence to support a definitive practice guideline concerning EGDT.

Institution of glycemic control (Grade 1B: strong recommendation, moderate evidence quality) *targeting a blood glucose < 150 mg/dL (8.3 mmol/L) after initial stabilization.* (Grade 2C.)
The Grade 2 guideline means that this component is "suggested" to clinicians. The Guidelines note there is insufficient evidence currently to support a recommendation for intensive glucose control (80–110 mg/dL [4.4–6.1 mmol/L]), but we note that there is also no evidence to enable a definitive guideline of < 150 mg/dL.

Intensive glycaemic control is supported by a single-centre randomised trial in surgical ICU patients.[4] There was a high mortality in the control patients, and an unusual feeding protocol, which made it difficult to generalise the findings to other locations. A subsequent

trial from the same group in medical ICU patients did not support the hypothesis.[5] There was sufficient uncertainty surrounding tight glucose control in the ICU to enable the NHMRC and the Canadian Institutes of Health Research to fund the 6100-patient, multicentre NICE-SUGAR trial, which will be completed in 2008–2009. Other multicentre randomised trials from Europe testing this hypothesis were stopped early because of safety concerns about hypoglycaemic events, and because of apparent futility.[6] It is conceivable that, when the large multicentre randomised trial is complete, a change in practice and clear practice guidelines might be warranted, but until then specific glycaemic control guidelines are premature.

Stress-dose steroid therapy given only in septic shock after blood pressure is identified to be poorly responsive to fluid and vasopressor therapy. (Grade 2C.)

The key data supporting this recommendation are from a study that did not find a significant decrease in landmark mortality.[7] Instead, the 2008 guideline arose from an adjusted analysis of a subgroup from the negative randomised trial. Further, the recently reported multicentre randomised trial of stress-dose steroid therapy for septic shock[8] found no difference in 28-day mortality in patients with septic shock who received steroids. Further trials are planned internationally, but in the meanwhile the literature does not provide clear guidance, and practice varies widely among Australian and New Zealand intensive care physicians. This practice variation seems likely to continue until more definitive clinical data are published.

Recombinant human activated protein C (rhAPC) in patients with severe sepsis and clinical assessment of high risk for death. (Grade 2B.)

This guideline is graded as "suggested" and of "moderate" quality. The supporting evidence is a single randomised trial,[9] in which the intention-to-treat analysis was positive, but there was considerable overall uncertainty.[10] The drug was subsequently licensed in the US for just one subgroup of high-severity patients, but the efficacy of rhAPC in this particular subgroup (for whom it is recommended in the 2008 Guidelines) has not been prospectively validated. Further, there have been safety concerns relating to potential bleeding in two negative rhAPC trials, which led to appropriate warnings to the Food and Drug Administration by the manufacturer. The European Medicines Agency has required a new randomised trial in high-risk patients, to confirm or refute the PROWESS[9] subgroup findings. There has been sufficient informed criticism of the PROWESS trial for ANZICS to be unable to recommend the use of rhAPC within practice guidelines.

Vasopressor preference for norepinephrine [noradrenaline] or dopamine, dobutamine inotropic therapy when cardiac output remains low despite fluid resuscitation and combined inotropic/vasopressor therapy. (Grade 1C.)

This guideline omits adrenaline, a widely used alternative vasopressor in Australia and New Zealand, and supports dopamine, which is rarely used as a primary vasopressor in our countries. No large studies have reported adrenaline to be inferior to either noradrenaline or dobutamine, and a recently completed comparative Australian trial found no difference between adrenaline and noradrenaline in ICU patients concerning resolution of shock.[11] Dopamine is not favoured in our countries, in part due to inferior potency as a primary vasopressor, in part due to adverse neurohumeral effects, and in part because a multicentre trial found that low-dose dopamine failed to improve outcomes in patients with sepsis.[12]

These five examples highlight the dynamic nature of the emerging evidence in ICU patients with sepsis and septic shock, and also highlight current Australian and New Zealand clinical research, which will help clarify some of the uncertainty.

Intensive care physicians in Australia and New Zealand strongly support the intentions of the *Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008* to provide best possible evidence-based guidelines for treatment of patients with severe sepsis and septic shock. ANZICS supports the consensus international view stated within the Guidelines that "Evidence-based recommendations regarding the acute management of sepsis and septic shock are the first step toward improved outcomes for this important group of critically ill patients". Many elements within the Guidelines are supported by ANZICS, including the intention of the Campaign that treatment of severe sepsis be delivered in a consistent and timely manner. A working party from the ANZICS Clinical Trials Group Executive will be formed to better define those elements within the Guidelines that are consistent with specialist practice in our region, as a safety and quality initiative. The considerations from this group will be formulated separately.

Nevertheless, ANZICS is concerned that the entire 2008 Guidelines package may be adopted in quality improvement programs in our countries. Sponsorship of the 2008 Guidelines by ANZICS would imply our support for the package in its entirety, and could enable criticism of clinicians who made a considered decision that substantive elements of the Guidelines were not in their patients' best interests. The decision not to sponsor was taken reluctantly by the ANZICS Board.

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