

## Sepsis outcomes have improved, but why?

Steven A R Webb

Sepsis is a major public health problem. In the United States, it is responsible by one estimate for as many deaths as acute myocardial infarction.<sup>1</sup> The reported case-fatality rate, which ranges from 25% to 50%, reinforces the substantial unmet need for new treatments that improve survival. The importance to public health is further emphasised by evidence from the US that sepsis is becoming more common.<sup>2</sup> In this issue of the Journal (*page 8*), the Australasian Resuscitation in Sepsis Evaluation (ARISE) Investigators and colleagues report that the incidence of community-acquired sepsis is also rising in Australia and New Zealand.<sup>3</sup> This is a valuable and informative study, which is uniquely possible as a consequence of the extensive data collected and maintained by the Adult Patient Database (APD) of the Australian and New Zealand Intensive Care Society.<sup>4</sup>

The conventional paradigm for improving outcomes in any disease is to identify new treatments, to evaluate them in well designed and adequately powered randomised control trials (RCTs), and then to implement those which have proven efficacy. For some decades, sepsis appeared resistant to this paradigm, with as many as 70 phase II or phase III RCTs before a positive study was reported. However, in recent years there have been several positive studies in sepsis or closely related conditions, including studies of activated protein C,<sup>5</sup> low-dose hydrocortisone and fludrocortisone,<sup>6</sup> tight glucose control in surgical patients,<sup>7</sup> lung protective ventilation in patients with, or at risk of, acute respiratory distress syndrome (ARDS),<sup>8</sup> and early goal-directed therapy (EGDT).<sup>9</sup>

Although the ARISE Investigators report a rising incidence of sepsis, there is also good news. In their representative sample of intensive care units in New Zealand and Australia, a progressive and clinically significant improvement in survival was observed over the 8-year study period from 1997 to 2005.<sup>3</sup> So, why is survival improving? Perhaps it is because the results of RCTs are being translated into practice. However, there is emerging doubt about the efficacy of low-dose steroids, as a consequence of the reported but not yet published Corticus (Corticosteroid Therapy of Septic Shock) study, and subsequent published and reported studies of tight glucose control have not shown a benefit.<sup>10</sup> Furthermore, tidal volumes for patients with ARDS in Australia average 9 mL/kg, rather than the 6 mL/kg shown to be of benefit in the ARDS Network study.<sup>11</sup> There is incomplete adoption of activated protein C,<sup>12</sup> and EGDT has not been imple-

mented in the region (Dr Sandra L Peake, Chair, ARISE Investigators, personal communication).

There are at least two alternative factors that may, at least in part, be responsible for the improved survival reported by the ARISE Investigators. Firstly, clinicians may just be getting better at using the same old therapies, a concept that has some support in the literature.<sup>13</sup> Secondly, it is possible that sepsis is being recognised earlier, in emergency departments and wards, so that treatment commences at a more favourable time in the natural history of the disease. Observational evidence about the critical role of early commencement of antibiotics in patients with septic shock provides a rationale for how better detection and recognition may improve outcomes.<sup>14</sup> The data collected and maintained by the APD is a rich and valuable resource, as evidenced by the ARISE study.<sup>3</sup> However, the observation that outcomes are improving in the absence of data of sufficient depth to allow exploration of possible associations, such as changes in therapy or presentation, is frustrating. There is much that might be learnt, for sepsis and many other conditions, from detailed observational data — so-called phase IV studies.

Uncertainty about the role that RCTs have played in improving outcomes should not be interpreted as a criticism of RCTs. Although RCTs are highly imperfect, they are and will remain indispensable for testing new treatments in the ICU. RCTs are the least biased way of evaluating effectiveness and are superior to all other methods of evaluation. However, as emphasised in several other articles in this issue of the Journal, RCTs are not the only method available for accumulating evidence of effectiveness. They are not suitable for all interventions, and they are limited by the quality of definitions used for inclusion and exclusion criteria.

For example, also in this issue of the Journal (*page 106*), Blyth and colleagues report a case of purulent pericarditis complicated by severe shock secondary to tamponade.<sup>15</sup> Prompt use of echocardiography was the key to diagnosis, which then led to relief of tamponade. Echocardiography can be extremely useful in the immediate investigation of severe shock,<sup>16</sup> and was demonstrated to be life-saving for this patient. But, there will never be Level 1 evidence from RCTs about the effectiveness of echocardiography. This case report is, and should be, sufficient to demonstrate effectiveness — a life was saved, and it was the echocardiogram that made the difference. Similarly, the review of extracorporeal membrane oxygenation (ECMO) by

MacLaren and Butt (*page 76*) serves to remind that this is an option for patients with refractory hypotension secondary to sepsis.<sup>17</sup> Anecdotally, refractory hypotension is becoming less common as a cause of death from severe sepsis, with most deaths arising from late and non-resolving multiple organ failure. While an RCT of ECMO for refractory shock would not be feasible, useful data about its use can, and should, be collected in national and international registries.

One of the many limitations of RCTs is the rigidity that comes from necessarily tight inclusion and exclusion criteria. The sepsis definitions developed by Roger Bone and others in 1991 remain widely used and at least offer the advantage of standardisation of inclusion criteria in sepsis trials.<sup>18</sup> However, these criteria have been rightly criticised for poor sensitivity and specificity.<sup>19</sup> An important additional limitation of the definition of septic shock is highlighted in the commentary in this issue of the Journal by Marik and Lipman (*page 101*).<sup>20</sup> Conventionally, septic shock is defined as “sepsis-induced hypotension persisting despite adequate fluid resuscitation”. This is sensible, as far as it goes, but critically limited by the absence of a definition of what is “adequate fluid resuscitation”. These authors make the sensible proposal of defining an adequate fluid challenge as 30 mL/kg. Although there is no empirical evidence presented to justify this choice, this was not a barrier to the adoption of the Bone criteria, which were validated only in retrospect.<sup>21</sup> What is needed now is evidence of how this, or alternative criteria, influence the impact of the definition. Such data may be available from the ARISE observational study of patients presenting with sepsis to emergency departments in 32 hospitals in Australia and New Zealand, which recently completed recruitment (Dr Sandra L Peake, personal communication).

Improving outcomes from sepsis is likely to be best achieved by advancing on all possible fronts: implementing new therapies for which good evidence exists, using standard therapies better, and diagnosing sepsis earlier. Many interventions are not suitable for RCTs, but evidence from case reports and registries can, and should, be used to guide clinical decision-making. Nevertheless, wherever possible, it is vital that proposed therapies, especially those that might be expensive or harmful, are evaluated by well designed and adequately powered RCTs. The call by the ARISE Investigators for a multicentre RCT of EGDT<sup>3</sup> is a particular imperative. Where RCTs are not possible, or there is not yet sufficient evidence to warrant an expensive trial, observational studies of large cohorts of patients with sepsis may be extremely useful. While the data maintained by the APD are particularly impressive, they are not sufficiently deep or broad to explore associations

between variation in practice and variation in outcome. Phase IV observational data could be particularly useful for generating new hypotheses and for evaluating the impact, in the real world, of newly introduced therapies.

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## EDITORIALS

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