

Surviving sepsis?

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Severe sepsis and septic shock represent the most extreme ends of the infectious diseases spectrum. Severe sepsis is generally defined by evidence of a systemic inflammatory response to an infection, with associated organ dysfunction (1). Patients who fulfill criteria for severe sepsis, who also have hypotension refractory to adequate volume replacement (ie, requirement for vasopressor support), are diagnosed with septic shock. Infection is considered to be the root cause for these conditions, and may be documented by positive cultures obtained from normally sterile body sites or clinically based on an integration of patient, laboratory and radiological data. A wide range of protozoa, bacterial, viral and fungal etiologies may result in severe sepsis and septic shock; the typical average case-fatality rate ranges from 30% to 50% (2).

After decades of extensive, but generally unsuccessful, attempts to find new and improved therapeutic strategies for severe sepsis and septic shock (3), the turn of the millennium witnessed the publication of a series of clinical trials showing significant and often dramatic mortality reductions associated with a range of different adjunctive and supportive treatment modalities (Table 1) (4-9).

These landmark clinical trials that demonstrated major mortality reductions led to a renewed optimism for improved therapy in patients with severe sepsis and septic shock, and were an impetus for the development of the Surviving Sepsis Campaign (10). The Surviving Sepsis Campaign was initiated by several international critical care societies to improve the recognition, management and outcomes of patients with severe sepsis and septic shock, with a mortality reduction goal of 25% associated with these conditions. This multifaceted initiative emphasized the use of 'bundles', in which elements of care identified through evidence-based literature review were grouped together along themes in an attempt to maximize the overall benefit. The Surviving Sepsis Campaign and management guidelines, initially published in 2004 under the auspices of the campaign, were widely accepted and adopted in vast numbers of intensive care units worldwide (11).

However, many of the results of these studies have been controversial (12), are under re-evaluation (13-15), or large multicentred trials have demonstrated either no or even adverse effects on mortality as shown in the final column of Table 1 (16-21). While there may be specific individualized instances in which the therapies listed in Table 1 may be appropriate for the management of patients with severe sepsis and septic shock, they may not be further considered to represent a standard of practice.

So should we be pessimistic about our present and future ability to improve the management of these seriously ill patients and consider the past decade of research and effort a bust? No. Ongoing efforts are being made to determine optimal means of resuscitation, and new pharmaceutical agents are in development and evaluation (15). However, the most important source of optimism we may have is that multiple lines of evidence indicate that the outcomes of severe sepsis and septic shock are continuously improving in high-income countries worldwide (22-25).

If one considers that we have made few evident major advances in severe sepsis and septic shock management in recent years, how could a reduction in the observed case-fatality rate (mortality) be reconciled? It is our opinion that observed improvements in outcome from

severe sepsis and septic shock in recent years reflect not the adoption of new therapies, but rather better application of previously existing modalities. There have been numerous observational studies that have reported significant improvements in mortality outcome following severe sepsis and septic shock, with the institution of sepsis bundles either locally developed or as recommended by the Surviving Sepsis Campaign (26-28). While studies that use a quasi-experimental (before/after) historical design must be interpreted with caution, bundled interventions appear to have had a significant overall effect on severe sepsis and septic shock outcome; this is largely due to improvements in general awareness and early recognition, improved resuscitation, early use of appropriate antimicrobials and attention to source control.

Although perhaps intuitive in retrospect, only during the most recent decade has the importance of prompt and effective antimicrobial therapy in improving septic shock outcomes become apparent. Although several publications have investigated this issue, the most recognized evidence is from a study based in Winnipeg, Manitoba. Using data from a large multicentred database, Kumar et al (29) showed that following the onset of hypotension, the adjusted OR for mortality associated with each 1 h delay in receipt of an effective antimicrobial was 1.119 (95% CI 1.103 to 1.136; $P < 0.0001$). General recognition by clinicians, and emphasis on prompt (generally defined as within 1 h of onset) treatment with antibiotics in sepsis initiatives, has undoubtedly led to earlier treatment of patients with severe sepsis and septic shock in recent years. In the analysis of more than 15,000 patients registered in the Surviving Sepsis Campaign database, early antibiotic therapy was one of the most important components associated with improved outcome (30).

It is also likely that patients with severe sepsis and septic shock are being recognized earlier and resuscitated more aggressively than in the past era. While adoption of the Rivers et al (5) early goal-directed therapy bundle has been met with considerable controversy, the need for prompt and thorough resuscitation has been widely accepted. Lactate measurements are now readily available as point of care tests in many centres and are routinely recommended by most sepsis guideline bundles. Their importance lies, in part, as a marker of severe disease, even in the absence of overt hypotension, and they may be used as a measure of resuscitation adequacy (5,14). The implementation of medical emergency teams in many jurisdictions may also play a role in the early detection and management of patients with severe sepsis and septic shock (31).

Attention to source control, and improvements in diagnostic tests and availability may also contribute to a reduction in severe sepsis and septic shock mortality. We anecdotally observe that prompt access to computed tomography scans and interventional radiology procedures have improved significantly over the past decade in Canadian centres, and this may be reflective of changes in other countries. Many centres have also instituted new tests, such as procalcitonin, and the availability of molecular laboratory diagnostics has flourished in recent years, resulting in earlier and more accurate identification of infections (32).

While we may be disappointed by the lack of new specific treatment modalities for severe sepsis and septic shock, at the end of the day, it is the outcome of patients that is the overriding consideration, and we are encouraged that outcomes do appear to be improving.

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TABLE 1
Landmark clinical trials reducing severe sepsis and septic shock at the turn of the millennium and current status

Intervention	First author, year (reference)	Design and intervention	Result	Current status
Activated protein C	Bernard, 2001 (4)	Multicentred, international, randomized, double-blind, placebo-controlled trial (RDBPCT) of activated protein C infusion versus placebo among 1690 patients with severe sepsis and septic shock	Significant reduction in all-cause mortality from 30.8% in the placebo group to 24.7% in the treatment group. Number needed to treat (NNT) to save one life was approximately 16	Numerous concerns raised about the original study results. The subsequent ADDRESS study (Abraham et al [16]) in lower-risk patients showed no mortality benefit but, a significant increased risk for bleeding. The trial results from high-risk patients of the PROWESS-Shock study (13) are pending; however, the drug has been withdrawn from the market
Early goal-directed therapy (EGDT)	Rivers, 2001 (5)	Single-centre trial comparing application of EGDT to usual care in 263 patients treated in the emergency department	Dramatic reduction in in-hospital mortality rate with EGDT of 30.5% versus 46.5%. NNT to save one life was approximately 6	Unclear if the specific components of treatment or bundle of treatments are of benefit (14), or whether these may reflect substandard treatment of control patients. Multiple international studies underway to assess further (15)
Intensive insulin therapy	van Den Berghe, 2001 (6)	Single-centre randomized trial comparing intensive insulin therapy (goal glucose level between 4.4 mmol/L and 6.1 mmol/L) versus control (goal between 10 mmol/L and 11.1 mmol/L) in 1548 ventilated surgical ICU patients	Significant mortality rate reduction from 8.0% in controls to 4.6% with intensive insulin therapy. NNT to save one life was approximately 29	Subsequent study by the same group in medical patients showed no benefit (17). The multinational NICE-SUGAR study (Finfer et al [18]) involving 6,103 patients demonstrated an increased mortality rate (27.5%) with intensive insulin therapy compared with conventional therapy (24.9%). NNT to cause one death is approximately 38
Low-dose corticosteroid	Annane, 2002 (7)	Multicentred French RDBPCT comparing low-dose corticosteroids with placebo in 229 patients with septic shock and relative adrenal insufficiency	Dramatic reduction in mortality rate with steroid therapy (mortality rate 63% in the placebo group versus 53% in the corticosteroid group; $P=0.02$). NNT to save one life was approximately 10	CORTICUS (Sprung et al [19]) is a multicentred international RDBPCT conducted in 499 patients who showed no overall mortality benefit in those with relative adrenal insufficiency, but there was an increase in complications
Renal replacement therapy	Ronco, 2000 (8)	A: A single-centre study randomly assigned 425 critically ill patients with renal failure to 20 mL/h/kg, 35 mL/h/kg or 45 mL/h/kg of ultrafiltration (groups 1, 2 and 3, respectively)	A: Groups 1, 2 and 3 mortality rates 41%, 57%, and 58%; NNT to save one life with dose 35 mL/h/kg or higher was approximately 6	A multicentred randomized trial (Palevsky et al [20]) of 1124 patients found no difference in mortality rate with an intensive versus conventional renal replacement strategy; A multicentre randomized trial (Bellomo et al [21]) of 1508 patients comparing 20 mL/h/kg versus 40 mL/h/kg of continuous renal replacement therapy found no difference in mortality rate
	Schiffli, 2002 (9)	B: A single-centre study randomly assigned 160 critically ill patients with acute renal failure to once daily or alternating day hemodialysis	B: Mortality rate of 28% for daily dialysis and 46% for alternate day dialysis. NNT to save one life was approximately 6	

ADDRESS study Administration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis study; CORTICUS study Corticosteroid Therapy of Septic Shock study; ICU Intensive care unit; NICE-SUGAR study Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation study; PROWESS study The Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis

Sepsis and septic shock remain deadly, underlining the importance of identifying new and better therapies and management strategies. We believe that there are two general messages that we may learn from the past decade regarding management of severe sepsis and septic shock, and that may apply broadly elsewhere. First, we must always remain skeptical and take care in rapidly adopting the results of single-centre studies that identify dramatic improvements in outcome, even if we are impressed by their publication in the highest impact

journals. Second, we must continuously remind ourselves that we may offer greater benefit to our patients by ensuring that we optimize treatments that we know are of benefit (either experientially or empirically proven) rather than focusing on 'new' or questionably proven therapies. Indeed, the core management principles of antibiotherapy, source removal and resuscitation have not changed since the 1960s; although collectively, they have yet to be mastered (3,33).

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