

Mortality in severe sepsis: an inconvenient truth

Rinaldo Bellomo

Over the Christmas period, I was on clinical duty for the intensive care unit and, as usual, cared for a number of patients with severe sepsis or septic shock. One patient had recently started chemotherapy for acute myeloid leukaemia and was now on a ventilator with acute respiratory distress syndrome (ARDS) and septic shock due to severe *Pneumocystis carinii* pneumonia. Another had septic shock and *Enterobacter cloacae* bacteraemia secondary to a pancreatic leak after a Whipple procedure for adenocarcinoma, with positive lymph nodes and resection margins showing invasive cancer. A third had invasive, biopsy-confirmed *Aspergillus fumigatus* pneumonitis, also following chemotherapy for acute leukaemia. The fourth had bacteraemia caused by multiresistant *Stenotrophomonas maltophilia* and vancomycin-resistant enterococci, and an intra-abdominal infection with multiresistant *Candida krusei* following a repeat liver transplantation. Quite a collection!

Amazing as it may seem (and certainly not because of my efforts alone), they were all alive when I handed over a week later. At a time of year that invited reflection, and in the midst of the ICU's involvement in the ARISE,¹ STATINS² and PROWESS SHOCK³ trials, the daily care of these patients prompted two thoughts. The first related to patient recruitment into sepsis trials. None of these patients with clear and irrefutable septic shock was recruited into any of the above trials. They could not be in ARISE because they had all come to the ICU from hospital wards rather than the emergency department. They could not be in STATINS because of exclusion criteria: abnormal liver function in two, an elevated creatine kinase concentration in another, and the inability to receive gastric feeding in the fourth, who therefore could not receive either placebo or atorvastatin. Finally, they could not be in PROWESS SHOCK — two because of severe thrombocytopenia, one because she had required repeated surgery, and the other because, in the presence of *P. carinii* pneumonia, ARDS, a Pao₂ of 58 mmHg and an Fio₂ of 0.8, even a fervent protagonist of trial medicine such as myself could not justify administering the fluid loading that arbitrarily defines “resuscitated” septic shock in that trial.

Thus, I found myself asking: given that none of my most severely ill patients with clear septic shock could be entered into any of the trials of septic shock currently recruiting in Australia and New Zealand, what does this say about trial design, trial relevance, and the applicability of trial findings to the patients I commonly see? And what does it say about the entire edifice of sepsis trials in the ICU? This is not an

idle end-of-year reflection — all three trials are having a hard time recruiting patients and are running well behind schedule. The patients with sepsis are there, sepsis is as big a problem — perhaps bigger — than ever. Yet, because of artificial rules, arbitrary time windows, non-validated definitions, and the absence of biomarkers and simple, universally applicable interventions, we can study only a small proportion of patients. Thus, we conduct underpowered studies (more about that below) and come up with results that might apply to just as small a proportion of patients as the proportion studied.

In our current research paradigm, the ideal clinical trial patient has no comorbidities, a life expectancy (assuming survival) that justifies the cost of the therapy in question, a clear disease time course, and, from presentation until recovery, has received optimal care, as defined some years ago by an international (but mainly US and European) committee. Why don't we study the patients we actually treat?

So, here is a thought for 2010: let the next chapter in the fight against sepsis by the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG) not be another trial, let it be the search for a biomarker or panel of biomarkers we can use as entry criteria for future trials. Let's just measure interleukin-6, or procalcitonin, or C-reactive protein, or all together, or some other relevant potential biomarker, and determine the cut-off levels we wish to use to select suitable patients with sepsis and suitable mortality. Let's get the test done as soon as possible in patients with clinically suspected sepsis, and then, if results exceed the necessary level(s), let's start treatment with the trial drug or placebo. It would never be perfect, some patients may turn out not to have sepsis, some patients with sepsis may be missed, but it would be better than what we do now. It would be reproducible, verifiable, quantitative and rapid, and it would allow a much broader range of patients to be included. By identifying patients earlier, we might even discover that interventions found wanting when applied only to patients with advanced disease are, in fact, of some use. We badly need to recruit more patients if we ever want to have sufficient power to detect clinical effects. Let's limit exclusions to those that would be useful to clinicians reading the trial results — essentially, patients in whom the intervention is contraindicated by its mechanism of action. The lesson of NICE-SUGAR is clear: we need to randomise more patients.⁴

So, in the absence of any biomarkers that satisfy us, if we were to conduct a trial of low-dose corticosteroids, let's have these inclusion criteria:

- The patient is in the ICU;
- The doctor thinks the patient has sepsis; and
- The doctor has started, or will now start, administering antibiotics.

And let's have these exclusion criteria: none!

The issue of power in sepsis trials and our inability to create broad criteria and capture sufficient patients also depends on the intervention we propose. Interventions that appear simple and safe can be applied to broader groups of patients because they have few exclusion criteria. The ANZICS CTG needs to explore all possible avenues for identifying simple and widely applicable interventions with minimal exclusion criteria, so that we exclude from trials only maybe <5%–10% of patients with sepsis, comparable to exclusions from large cardiology trials. We need to identify all simple interventions that, after testing in animals and in phase I pilot studies, appear efficacious and, by consensus, choose the one or two we can take to phase IIa and, if appropriate, phase IIIb trials. We must emulate pharmaceutical companies, which are dedicated to developing generic products for mass consumption; we need to develop a process to identify and develop generic products that justify large trials.

The concept of the "large trial" takes me to my second Christmas reflection, which has been in my mind for some time but was rekindled by my four patients. These patients will have either survived or died (I will find out when I get back), and they did have sepsis, but any deaths would be only partly attributable to sepsis. These patients had leukaemia, cancer, immunosuppression, to name just a few other major contributors to their mortality risk. Thus, when we say the mortality of patients with severe sepsis is perhaps 30%,⁵ although technically correct, we omit an inconvenient truth: much of that mortality is not attributable to sepsis. This is deeply inconvenient because any treatment directed at the septic process cannot possibly undo the mortality risk attributable to age, cancer, immunosuppression, longstanding organ dysfunction and so on.

In that case, what percentage of the 30% mortality of severe sepsis is amenable to manipulation? The precise answer would require complex statistical calculations of attributable risk and relative mortality.^{6–8} However, one can make a simple approximation by considering patients with severe sepsis or septic shock whose age (<44 years) does not independently increase the risk of death in illness severity scores, and who have no comorbidities that also independently increase risk of death (such as AIDS, hepatic failure, lymphoma, leukaemia and immunosuppression).

These patients might be said to have "only sepsis" as their cause of ICU admission, and thus have a mortality reasonably attributable to sepsis alone. Of course, this is an oversimplification, as many are likely have other less severe comorbidities (such as asthma, ischaemic heart disease, hypertension and diabetes) that might also contribute to their risk of death. And, of course, there may be unrecorded — or even unobservable — reasons they developed sepsis in the first place. Thus, this simple approach would most likely overestimate the true attributable mortality of sepsis. However, this is useful as, whatever the findings, one could not be accused of underestimating the risk of sepsis.

Armed with these concerns, I asked Professor Michael Bailey at the Australian and New Zealand Intensive Care Research Centre to help. He used the Centre for Outcome and Resource Evaluation (CORE) database for ICU patients for 2006, 2007 and 2008 and the appropriate APACHE III codes to establish the mortality of patients with sepsis aged <44 years with no major comorbidities. The answer: 10.27%.

This finding should not be surprising. Moreover, it is identical to the mortality of severe sepsis in the paediatric population, where comorbidities are less common,⁹ providing further support. If 10% absolute mortality is the modifiable component of the risk of death in ICU patients with sepsis, and if an intervention leads to a 25% relative reduction in mortality, then the absolute change in mortality that we need to detect is actually about 2.5% (number need to treat = 40). Thus, sepsis trials for the next decade should logically be powered to detect a decrease in mortality from 30% to 27.5%, maybe even less. Another inconvenient truth is therefore that, unless sepsis trials randomise > 8000 patients, or the effect is much greater than a 25% relative risk reduction (which is unlikely), trials will never have a positive result, and, if they do, we should seriously worry that it is a false positive.

The corollary of the above observations is that positive results from sepsis trials involving small numbers may well be an illusion,^{10,11} and that ARISE, its American counterpart (PROCESS), and PROWESS SHOCK, and all other ongoing phase III sepsis trials, will likely give negative results. More importantly, as long as trials exclude the majority of patients with sepsis, no single funding jurisdiction will be able to conduct trials of the necessary size to detect such small absolute differences. The only logical conclusion is that novel approaches are needed: simple interventions, highly pragmatic trials with minimal data collection burdens, collaborations across jurisdictions, synchronised and equivalent-protocol trials in different jurisdictions with subsequent meta-analysis of individual patient data,¹² or recruitment of regions with large populations and emerging ICU structures.

EDITORIALS

In the first decade of this millennium, the ANZICS CTG blazed a trail, showing the intensive care world the importance of large pragmatic trials. May the New Year resolution for the second decade see the ANZICS CTG apply simple pragmatic trials to the treatment of severe sepsis.

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