Infections in the intensive care unit — important questions remain

David L Paterson and Jeffrey Lipman

How do we address the significant mortality of patients with sepsis presented in this issue of the Journal (*page 8*) by the Australasian Resuscitation in Sepsis Evaluation (ARISE) Investigators and colleagues?[1] Their study of around 100 intensive care units in Australia and New Zealand found a 20.9% ICU mortality and 27.6% hospital mortality among patients with sepsis.

Apart from resuscitation,[2] potential ways of improving the outcome from sepsis are by optimising:

- the adequacy of the antimicrobial regimen;
- the timeliness of the antimicrobial regimen;
- the specific nature of adjunctive supportive regimens; and
- the adequacy of follow-up care.

Other reports in this issue illustrate the importance of addressing each of these aspects. For example, MacLaren and Butt discuss the role of extracorporeal membrane oxygenation in adjunctive management of sepsis (*page 76*).[3] In addition, Litton and colleagues address in-hospital mortality after ICU discharge and how this may best be predicted (*page 19*).[4]

Australian and New Zealand ICUs are ideally placed to address many of these dilemmas. We will briefly examine the first suggestion above — improving the adequacy of the antimicrobial regimen — and make recommendations as to how this may best be achieved. The other suggestions could be similarly addressed, stemming from some of the research presented in this issue.

There is mounting evidence that the adequacy of the antimicrobial regimen used in patients in the ICU is an independent predictor of survival.[5] The most common reasons for inadequate antimicrobial regimens are:

- failure to consider the potential for an antibiotic-resistant organism in an initial empirical regimen;
- failure to consider specific types of organisms (eg, *Pseudomonas aeruginosa*, and *Enterococcus* and *Candida* spp.);
- "under-dosing"; and
- failure to prevent subsequent emergence of multiresistant organisms.

The potential for antibiotic-resistant organisms is best recognised through consideration of local epidemiology, which demands close collaboration between intensivists and clinical microbiologists. We need more research on how to maximise the spectrum of initial empirical regimens while avoiding unnecessary selection of resistant organisms. Risk factors for specific organisms need to be assessed through review of the literature and, preferably, locally oriented case–control studies. Chatterjee and colleagues, in this issue (*page 69*), start to address a specific organism, *Enterococcus*, by performing a literature review and formulating recommendations as to which patients should receive enterococcal coverage.[6]

We believe that under-dosing of antimicrobial agents is common in Australasian ICUs. Under-dosing refers to both the dose and frequency of administration. In-vitro studies suggest that certain pharmacodynamic targets should be met to optimise the likelihood of bacterial eradication.[7] Randomised trials should be performed to determine whether theoretical pharmacodynamic or microbiological principles truly make a difference to patient outcome.

Multiresistant bacteria continue to emerge throughout ICUs worldwide. Combination antimicrobial regimens have prevented the emergence of resistance in tuberculosis and HIV infection, but it may be naive to believe that this principle applies to bacterial infections in general. This may represent an important avenue for study. "De-escalation" is a relatively new term for an approach that aims to optimise initial antibiotic choices while preventing subsequent emergence of antibiotic resistance.[8] Again, formal study of this approach is important to determine whether it makes any difference to patient outcome. Finally, restricting the duration of antibiotic use may relieve the selection pressure which is likely to contribute to antibiotic resistance, but this can be advocated only if accompanied by resolution of infection without relapse. Randomised trials of two durations of antibiotic regimens can surely answer such questions.

We live in exciting times in the critical care community. Clinical collaboration between intensivists and specialists in many medical and surgical disciplines is commonplace. Within the Australian medical community, there is now an emerging opportunity for research collaboration between intensivists and specialists in a variety of fields. Studying patients with sepsis is likely to be a fruitful example of such an approach.

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