Confronting the threat of multidrug-resistant Gram-negative bacteria in critically ill patients

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The re-emergence of infection due to multidrug-resistant Gram-negative bacteria in critically ill patients presents particular challenges to clinicians, given the lack of a pipeline of new antibiotics active against these resistant strains. Infected patients have a worse outcome than non-infected patients, although the additional contribution of antimicrobial resistance is less easy to define. Newer and better antibiotics would be welcome, but are unlikely alone to make a major impact on clinical outcomes.

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Introduction

Patients on an intensive care unit (ICU) are frequently infected, and infected patients have a higher mortality than those who are uninfected.\(^1\) Compelling evidence of the problem, if more evidence is needed, comes from two recent large studies that have clearly documented the scale of the challenge. Lagu et al.\(^2\) studied US patients hospitalized for sepsis during the period 2003–07 and documented a 71% increase in admissions. Furthermore, there was evidence that there was a steady increase in the severity of the illness in these patients: the proportion of patients with three or four or more organ dysfunctions increased 1.2- and 1.5-fold, respectively (P<0.001), although interestingly there was a very slight drop in mortality over the same period. The second study was EPIC II, a point prevalence analysis that surveyed 14 414 patients on 1265 ICUs worldwide.\(^3\) On the day of the study, just over half the patients were considered to be infected and >70% were receiving antibiotics (an interesting figure in itself). Strikingly, 62% of the microbial isolates were Gram-negative bacteria, a reversal of the pattern seen in previous studies, in which Gram-positive bacteria predominated. Both the ICU mortality and the hospital mortality were more than twice that of non-infected patients. Infection on the ICU, in particular with Gram-negative bacteria, evidently remains a significant challenge.

The challenge of multidrug resistance (MDR)

The challenge is compounded, of course, because of the fact that Gram-negative bacteria often demonstrate MDR. Organisms such as Pseudomonas aeruginosa, Acinetobacter spp. and species that produce extended-spectrum β-lactamases are disproportionately common on ICUs and it is these that present the biggest challenge, although there are marked geographical variations. For example, rates of Acinetobacter infection ranged from 3.7% in North America to 19.2% in Asia.\(^4\) There is also no doubt of the paucity of new antibiotics coming on stream that have activity against these MDR Gram-negative bacteria,\(^5\) or of the relentless evolution of ever more ingenious mechanisms of antibiotic resistance, the New Delhi metallo-β-lactamase being the most obvious recent example.\(^6\) What is perhaps slightly less clear, though, is whether antibiotic resistance per se is responsible for increasing the mortality of ICU patients.\(^7\) Or, put another way, are you more likely to die from an MDR Gram-negative infection than from an infection with a susceptible strain, all other things being equal?

In EPIC II, multivariate analysis demonstrated that infection with Acinetobacter spp. was associated with a greater risk of hospital death, and the authors comment that ‘given the high level of resistance of Acinetobacter to many antibiotics…this pathogen presents a continuing challenge in today’s ICU’. This is true, but does not quite get at the question of cause and effect, the so-called attributable mortality. To try to address this, Lambert et al.\(^6\) have recently reported an analysis of nearly 120 000 patients admitted to over 500 ICUs in 10 European countries. After controlling rigorously for multiple confounding factors, their data confirmed the EPIC II result, showing that the risk of death was two to three times higher for exposed (i.e. infected) rather than unexposed patients (hazard ratios between 1.7 and 3.5), depending on the microorganism and the site of infection. However, what was particularly interesting was that they went on to analyse the independent effect of antibiotic resistance. By comparing paired outcomes in infections with susceptible or resistant strains of the same organism they showed that the additional effect of the presence of antibiotic resistance was modest—hazard ratios were 1.2–1.6. Curiously, the exception was Acinetobacter baumannii, where the hazard ratio for ICU death comparing resistant with susceptible strains was in fact 0.8. But this is an exceptionally difficult area to study; others have concluded that
third-generation cephalosporin resistance in *Escherichia coli* does lead to increased mortality.7

Management of infection in the ICU

Data such as those above are not just of intellectual interest. Clinicians working on the ICU are routinely faced with the dilemma of how best to square the circle of providing the most appropriate empirical antibiotic therapy for their patients without at the same time driving the emergence of yet more resistant bacteria.8 These concerns are driven by studies that demonstrate that prompt, appropriate antibiotic therapy lessens mortality9 and by the recommendations of groups such as the Surviving Sepsis Campaign, who advocate empirical combination therapy targeting Gram-negative bacteria, in particular where there are concerns about the risk of *P. aeruginosa* infection.10 There is a danger that our only response to the threat of MDR Gram-negative bacteria will be to conclude, albeit reluctantly, that we desperately need ever better, ever stronger antibiotics and in the meantime we will have to use the most broad-spectrum agents available to us.

But that is not the only way. To paraphrase, it is not antibiotic resistance genes that kill people, it is bacteria. Last year, a rather grandly named ‘Gram-negative Resistance Summit’, convened in the USA, explored the evidence supporting a range of different clinical strategies designed to confront this problem (Figure 1).11 Although the data supporting these strategies—and the acceptance of them—were variable, they underline the fact that we need to focus on obtaining more and better evidence to inform our practice.12

Understanding the impact of MDR in Gram-negative bacteria helps to contextualize the choices we must make. A steady stream of new antibiotics aimed at MDR Gram-negative bacteria would be welcome, but this alone might make a relatively modest impact on clinical outcomes. Much more effective would be innovative approaches to reducing the likelihood of colonization and subsequent infection, thereby reducing both the need to use antibiotics at all and the constant pressure leading to multiple antibiotic resistance. Such strategies are likely to be more effective in the long term than relying on a pipeline of antibiotics that will only ever have a limited lifespan.

Figure 1. Possible strategies to deal with the problem of MDR Gram-negative infections in critically ill patients.11 Reproduced with permission.