Introduction: treatment of Gram-positive infections

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It is fascinating to look back over the past 20–30 years and see how the major hospital pathogens have changed. Staphylococci and streptococci were prevalent in the 1960s and 1970s; the major Gram-negative organisms increased in importance in the 1970s and 1980s; and now, the Gram-positive organisms have re-emerged as major hospital pathogens. In large part this trend may be attributed to the selection pressure created by antibiotics used in hospitals. The early penicillins were replaced by the broad-spectrum cephalosporins and fluoroquinolones. Currently, the most common pathogens isolated in the intensive care unit (ICU) are the coagulase-positive and -negative staphylococci (Figure 1).1 In some institutions Enterococcus spp. are now more prevalent than Pseudomonas aeruginosa.

The rates of nosocomial infection are fairly consistent across Europe.2 However, the prevalence of infection within ICUs differs considerably across European countries, from approximate rates of 10% and 11% in Switzerland and Scandinavia, respectively, to 31% and 32% in Greece and Italy, respectively (Figure 2).3 The reasons behind these differences are difficult to assess and no doubt reflect the types of patients admitted as well as the available resources. What is undeniable is that the European Prevalence of Infection (EPIC) study found that 45% of 10038 enrolled patients were infected.3 By any measure, this rate is unacceptable.

In addition to the change in causative organisms over time, a shift in antimicrobial resistance has become evident. During the past 20–30 years, there has been a vast increase in our understanding of how adept bacteria are in adjusting to antimicrobials, not just by mutation, but by plasmid and transposon exchange, DNA transformation and bacteriophage transduction. No antimicrobial exists to which some bacteria have not become resistant. As stated earlier in the context of ICU infection prevalence, there are considerable differences in resistance patterns across Europe. For example, prevalence rates of methicillin-resistant Staphylococcus

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 aureus (MRSA) among *S. aureus* isolates vary from approximately 50% in Greece to negligible levels in Sweden and Denmark (Figure 3).\(^4\) Other examples are the differences observed in enterococcal resistance to vancomycin: resistance rates are modest in Europe but represent a major problem in the USA. Again, whether these differences are related to infection control activities, antimicrobial selection pressure or available resources is often poorly understood. What is undeniable is that, together with enhanced infection control, there is a need for both new treatments and new approaches to therapy.

Current management of the major clinical conditions in which Gram-positive cocci tend to be prevalent typically includes the use of a β-lactamase-resistant penicillin (in Europe, usually flucloxacillin), a cephalosporin, or in the case of enterococcal infections, ampicillin or a similar agent. Because of high acquired resistance rates or relatively poor intrinsic activity, macrolides and aminoglycosides tend to be less widely used. It is interesting to speculate whether the widespread use of these latter agents has assisted in selecting for MRSA. In this supplement Livermore will discuss in some detail the various mechanisms of resistance encountered in Gram-positive cocci as well as the spectrum of action of the new oxazolidinone, linezolid.

Over the past few years we have learned how to employ antibiotics more effectively to maximize efficacy and reduce the likelihood of the emergence of resistance. Pharmacokinetics and pharmacodynamics are discussed in the article by...
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MacGowan. The bioavailability, degree of metabolism, penetration to sites of potential infections and mechanism of excretion of an agent are all important prerequisite knowledge for using antibiotics appropriately. Similarly, knowledge of how the bacteria and drugs interact can lead to the most advantageous mode of administration. The availability of both oral and intravenous forms of linezolid is of significant clinical and economic importance, as both MacGowan and Nathwani emphasize.

Appropriate antibiotic therapy is essential to good clinical management. For example, the correct choice of an antibiotic (i.e. one to which the infecting organism is susceptible) is associated with a much greater chance of clinical success than an inappropriate choice. Kollef et al. have demonstrated that in an ICU, mortality was twice as high when inadequate treatment (as defined by the pathogen’s lack of susceptibility) was given compared with adequate therapy (25.8% compared with 12.2%). Another study in bacteremic patients has shown a comparable difference. Similarly, delays in instituting therapy are associated with increased mortality. Therefore, the emerging message is to ‘get therapy right the first time’.

The ability to be correct in the antibiotic choice for Gram-positive infections is, as has been pointed out, confounded by the increasing problem of resistance. The use of new agents or combinations of agents that are active against these pathogens may address the problem. The role of glycopeptides, streptogramins and oxazolidinones needs to be carefully evaluated. Wilcox and French will discuss the clinical efficacy and safety of linezolid, the first of a truly new class of antimicrobials, the oxazolidinones.

In choosing an empirical regimen that favours a new antibiotic over older agents, cost is often an issue. New agents tend to be more expensive than older ones, and antibiotics account for a sizeable amount of all hospital drug budgets. Nathwani addresses this issue in a comparison of linezolid with an established agent, vancomycin, in hospitalized patients with methicillin-resistant staphylococcal infections. He also explores the costs and benefits associated with reducing hospital length of stay.

The battle against Gram-positive pathogens requires a multidisciplinary approach. This supplement discusses the issues in the light of new advances in antimicrobial chemotherapy. Prompt administration of appropriate therapy is key to the effective management of Gram-positive infections.

References
