Infections with Gram-positive bacteria in the immunocompromised: problems and solutions
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The last decade has witnessed a significant swing towards serious infection caused by gram-positive bacteria especially those that have developed resistance to a variety of antibacterial agents. This change has had a profound effect on the treatment options available especially for immunocompromised patients. Such patients are especially at risk of life-threatening bacteraemic episodes caused by staphylococci and enterococci in particular.

Many hospitals are experiencing underlying levels of infection with these bacteria approaching 30-35%. Notably we recognise methicillin-resistant *Staphylococcus aureus* (MRSA) often with additional antibiotic-resistance determinants (including that to the glycopeptides) and vancomycin resistant *Enterococcus faecium* and *E. faecalis*. Even the once susceptible *Streptococcus pneumoniae* has now developed resistance to penicillin and erythromycin. Increased usage of antibiotics in hospitals and elsewhere has exerted selective pressure on Gram-positive pathogens especially resulting in an increased incidence of multiresistant strains.

In response there has been renewed interest in antibacterial agents whose spectrum of activity is focused mainly on staphylococci and streptococci. For example, good activity has been demonstrated with a streptogramin complex, an oxazolidinone, a ketolide, a quinolone, and a lipopeptide. It should be noted that each of these agents (apart from the ketolide and quinolone) are novel compounds with new modes of action and therefore less likely to develop resistance mechanisms provided they are used conservatively in treatment. Nevertheless we are only too aware that resistance will develop to these agents; indeed long-term therapy of an immunocompromised patient is likely to trigger development of such resistance.

Does the resistance epidemiology demand new antibiotics?
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Multiresistance is increasingly prevalent in many pathogens, although the extent of the problem varies hugely between countries, hospitals, and units within hospitals. Resistance rates are notoriously highest in many newly prosperous developing countries and in those milieux where antibiotic use is of necessity high intensive care units. Counterwise, resistance rates are generally low in Scandinavia and the Netherlands. In the case of gram-positive pathogens, concern about resistance centres upon the mounting prevalence rates of methicillin-resistant staphylococci (MRSA) vancomycin-resistant enterococci (VRE) and penicillin/macrolide-resistant pneumococci. Among gram-negative bacteria the greatest concerns are the small but growing numbers of *P. aeruginosa* and *A. baumannii* isolates that are now susceptible only to polymyxins.

MRSA presently account for over 30% of *S. aureus* isolates from bacteremias in the USA, East Asia, much of southern Europe, the UK, and Eire. Within these countries, most MRSA infection is clonal and reflects cross infection rather than new evolution. Thus, for example, the explosion in MRSA rates in the UK in the mid-1990s was co-incident with the emergence of two new “epidemic” strains, EMRSA 15 and 16, and these now account for over 95% of MRSA bacteraemias in the country. MRSA have a variable range of resistances to other drugs, dependent on the particular strain; they mostly remain susceptible to glycopeptides, although resistance is occasionally reported, particularly to teicoplanin. VRE have a broader spectrum of resistance than MRSA, not least because most of the vancomycin resistance is concentrated in *E. faecium*, a species with inherent resistance to all β-lactams, as well as frequent acquired resistance to other drug classes. Among *E. faecium* isolates, high vancomycin resistance rates (>25%) are seen in the USA, UK and Spain whereas rates are low in Scandinavia and, more surprisingly, in Southeast Asia. Vancomycin resistance is 10-fold less frequent in *E. faecalis* than *E. faecium*, but does seem to be increasing in the UK and USA, especially among isolates from more serious infections. In the case of *S. pneumoniae*, the major problem is the international spread of a few lineages, mostly of serotype 6, 9, 14, 15, 19 and 23, with resistance to penicillin, macrolides and tetracyclines. These are highly prevalent in Southeast Asia, the USA, and southern Europe but much scarcer in northern Europe (except Eire).

Part of the response to multiresistance must lie in the better and lesser use of antibiotics together with—especially against MRSA—better infection control within hospitals. Experience, however, suggests that any decline in resistance achieved by these measures will be slow and uncertain. For that reason, continued antimicrobial development remains vital and, despite recent concerns, is continuing. In particular, new anti-gram-positive agents are being developed and launched: quinupristin/dalfopristin and linezolid have become available during the past two years whilst daptomycin, tigecycline and oritavancin are anticipated during the next three. Of the two agents recently launched, quinupristin/dalfopristin is widely active against gram-positive
Staphylococci except *E. faecalis*, although a few strains of staphylococci and *E. faecium* with acquired resistance contingent on efflux or acetylation of dalfopristin. Linezolid has near-universal activity against gram-positive cocci, with MICs narrowly distributed from 0.5 – 4 mg/L. Linezolid-resistance has only been encountered in a few mutants of enterococci and one MRSA, virtually all of them selected during therapy in underdosed patients or those with indwelling devices or difficult-to-reach infections.

Agents such as linezolid give vital new options against gram-positive bacteria. Increasingly, therefore, the centre of concern must swing back to gram-negative bacteria, where pan-resistance is emerging in a few non-fermenters – mostly *P. aeruginosa* from cystic fibrosis in the West, but more widely among pseudomonads and *Acinetobacter* spp. in East Asia. Against these organisms there is a dearth of advanced antimicrobial developments although carbapenemase inhibitors, efflux inhibitors and antimicrobial peptides all provide prospects for the more distant future.

**Understanding antibiotic resistance development in the immunocompromised host**

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Infections with a variety of agents cause major problems in the immunocompromised host. In addition to infection control techniques, a number of strategies utilizing antimicrobial agents have been employed: therapeutic use for documented infections; preemptive use for suspected infections; and prophylactic use to prevent infection in high-risk patients. Among the major risk factors for bacterial infections in the immunocompromised host are neutropenia, breakdown in mucosal protective barriers secondary to immuno-suppressive agents, and contamination of surgical procedures (especially in solid organ transplants) as well as the further immunosuppressive effects of opportunistic (especially viral) infections. It is the use of antimicrobial agents in this setting that is the major factor in selecting for resistant bacteria. In some cases, the organisms emerge because they are not included in the spectrum of activity of the drug being utilized. In other cases, antibiotic use results in the selection of resistant bacteria originally in the spectrum of the agent being utilized. Examples of this are seen in the studies in which earlier generation fluoroquinolones (which lacked outstanding coverage against Gram-positive bacteria) were used for prophylaxis in neutropenic patients; and as a result of this, the patients undergoing such prophylaxis showed a marked increase in incidence of infections due to viridans streptococci.

The addition of penicillin to the regimen initially suppressed the viridans streptococcal infections, but resulted in the emergence of penicillin-resistant viridans streptococci. Indeed, it is often possible to predict the organisms likely to emerge in the setting of extensive antimicrobial use for therapy or prophylaxis. Extensive use of expanded-spectrum cephalosporins often results in the emergence of *Enterobacter cloacae, Enterobacteriaceae* with extended-spectrum beta-lactamas, vancomycin-resistant enterococci, and nonfermenting organisms such as *B. cepacia, Acinetobacter* species, etc. The use of beta-lactam/beta-lactamase inhibitors often results in the emergence of MRSA, or *Enterobacteiaceae* with inhibitor-resistant beta-lactamas. Substituting carbapenems also selects for MRSA, *Sienotrophomonas malophilia, Serratia marcescens* with carbapenemases, or vancomycin-resistant *Enterococcus faecium*. As noted before, the earlier generation fluoroquinolones often selected Gram-positive organisms, but the newer fluoroquinolones can select for MRSA, or fluoroquinolone-resistant *Enterobacteriaceae* and/or *Pseudomonas aeruginosa*. Extensive use of vancomycin or teicoplanin is responsible for the emergence of vancomycin-resistant enterococci and strains of *S. aureus* with intermediate resistance to glycopeptides (GISA). Many of these organisms are Gram-negative, but the Gram-positive bacteria have become a major problem in the immunocompromised host in recent years. Among the important Gram-positive organisms causing problems in this setting are methicillin- and fluoroquinolone-resistant *S. aureus*, methicillin-resistant coagulase-negative staphylococci, beta-lactam-resistant viridans streptococci, and vancomycin-resistant enterococci. Interestingly, three of the four of these organisms are bacteria that are usually considered to be of relatively low virulence and are part of the normal human bacterial flora. However, it is the resistance to antimicrobial agents in these organisms that makes them dangerous in the immunocompromised host.

The development of resistance to antimicrobial agents in bacteria occurs by one of two mechanisms: chromosomal mutation or dissemination of resistance genes among microorganisms. These two mechanisms of resistance have clinical significance. Emergence caused by chromosomal mutation is a rare event and is stable when it occurs. It involves a single strain, a single resistance gene and is selected for at the site of infection. It is selected by a specific antimicrobial given to a specific patient and the resistant clones can lead to therapeutic failure or disseminate through cross-infection. Antibiotic combinations may prevent the selection of resistance due to chromosomal mutation. On the other hand, resistance related to the dissemination of resistance genes among microorganisms (eg, plasmid- or transposon-mediated resistance) is a relatively frequent event and of variable stability. It involves two strains of bacteria and often involves multiple resistance determinants. Selection is frequently at a site other than that of