Journal of Antimicrobial Chemotherapy (1997) **39**, *Suppl. A*, 1–6

JAC

Gram-positive resistance: challenge for the development of new antibiotics

Fernando Baquero

Departamento de Microbiología, Ramón y Cajal Hospital, Madrid, Spain

The incidence of infections caused by multidrug-resistant Gram-positive organisms is increasing despite advances in antibacterial therapy over the last 20 years. As the pathogens causing these infections are frequently resistant to most currently available antibacterials, they are extremely difficult to treat. Problematic pathogens include strains of *Streptococcus pneumoniae* resistant to β-lactams and macrolides, viridans group streptococci resistant to β-lactams and aminoglycosides, enterococci resistant to vancomycin and teicoplanin and highly resistant to penicillins and aminoglycosides, and *Staphylococcus aureus* resistant to methicillin, other β-lactams, macrolides, lincosamides and aminoglycosides. Other important pathogens include *Streptococcus pyogenes* resistant to macrolides (and suspected to be resistant to penicillin), macrolide-resistant streptococci of groups B, C, and G, coagulase-negative staphylococci resistant to β-lactams, aminoglycosides, macrolides, lincosamides and glycopeptides, multiresistant strains of *Listeria* and *Corynebacterium* and Gram-positive anaerobes, such as *Peptostreptococcus* and *Clostridium*, resistant to penicillins and macrolides. Thus, there is an urgent need for new antibacterial agents that are able to overcome multidrug-resistant mechanisms. The novel semisynthetic injectable streptogramin quinupristin/dalfopristin offers the prospect of effective treatment against many of the above pathogens.

Introduction

The incidence of serious bacterial infection is increasing despite remarkable advances in antibiotic chemotherapy. Of great concern is the increasing incidence of infections caused by Gram-positive bacteria with acquired multidrug resistance. The increase in resistant Gram-positive strains may be explained, in part, by scientists concentrating in the 1970s and 1980s on the development of drugs active against Gram-negative pathogens, thereby permitting the slow evolution and selection of resistant Gram-positive bacteria.

Antibacterial agents may be rendered inactive by three major mechanisms: destruction or modification of the antibiotic (e.g. production of β-lactamases and aminoglycoside-inactivating enzymes), prevention of access to the target (e.g. alteration of permeability or efflux) and alteration of the target site. These mechanisms of resistance in Gram-positive bacteria can be mediated either via chromosomes or via plasmids (Table I). For example, a chromosomally mediated genetic determinant known as *mec*, which facilitates the production of new DNA and causes alterations in penicillin-binding proteins (PBPs), is responsible for the methicillin resistance expressed by *Staphylococcus aureus*. PBP 2′, the PBP contained in methicillin-resistant *S. aureus* (MRSA) isolates, has a lower affinity for, and binds less avidly to, β-lactam drugs than normal PBPs and thus prevents β-lactams from interfering with cell wall synthesis.[1] Penicillin resistance in *Streptococcus pneumoniae* develops through a similar mechanism, although the production of PBP 1a, PBP 2b and PBP 2x appears to occur through gene mutation rather than production of new DNA.[1] In contrast, *Enterococcus faecium* resistance to vancomycin evolves through the acquisition of new DNA on plasmids or chromosomes;[1] this prevents vancomycin from disrupting cell wall synthesis.[1]

At present, the range of available antibacterials which are effective against Gram-negative infections is significantly greater than the range effective against Gram-positive pathogens. Thus, researchers are faced with major challenges to develop drugs effective against problematic Gram-positive organisms, including penicillin- and macrolide-resistant pneumococci, viridans streptococci resistant to β-lactams and aminoglycosides, vancomycin- and teicoplanin-resistant enterococci and MRSA.

Table I. Gram-positive pathogens with increasing resistance to antibacterial agents

Organism	Antibacterial resistance to
S. pneumoniae	β-lactams and macrolides
Viridans streptococci	β-lactams and aminoglycosides
Streptoccus pyogenes	macrolides and possibly penicillins
Groups B, C and G streptococci	penicillins, macrolides and aminoglycosides
Enterococci	glycopeptides (vancomycin, teicoplanin), penicillins and aminoglycosides
S. aureus	β-lactams, aminoglycosides, macrolides and lincosamides
Coagulase-negative staphylococci	β-lactams, aminoglycosides, macrolides, lincosamides and glycopeptides
Listeria spp. and *Corynebacterium* spp.	multidrug resistance
Gram-positive anaerobes (*Peptostreptococcus* spp., *Clostridium* spp.)	penicillins and macrolides

Streptococci

Pneumococci

Infections caused by *S. pneumoniae*, including pneumonia, meningitis, bacteraemia, sinusitis and otitis media, are extremely common, and their associated morbidity and mortality place a tremendous financial burden on society (estimated expenditures of over $4 billion/year in the USA).[2]

The incidence of infections caused by penicillin-resistant pneumococci has greatly increased in recent years, thereby complicating the management of these infections.[3] Highly resistant strains (MIC >2 mg/L) may fail to respond to penicillin or ampicillin therapy, particularly in locations where the antibiotic concentration is limited, such as the cerebrospinal fluid. These strains frequently have increased MICs for alternative agents commonly prescribed for the empirical therapy of meningitis, including extended-spectrum cephalosporins and chloramphenicol.[4]

Otitis media caused by penicillin-resistant pneumococci is also a problematic infection to treat. Amoxycillin is the drug of choice for this condition, yielding the lowest MIC against penicillin-susceptible and -resistant strains, but the difficulty of getting sufficient concentrations in the middle ear may lead to higher rates of failure,[3] frequently reflected as an increase in the number of recurrences. Of the oral cephalosporins, cefpodoxime and cefuroxime had the lowest MICs, but these are one to four dilutions higher than those of amoxycillin against *S. pneumoniae* strains that have either intermediate resistance or resistance to penicillin.[5] In the USA, the Centers for Disease Control reported an incidence of penicillin-resistant *S. pneumoniae* of 5% in the period 1979–1987; however, this has increased markedly in recent years with 15.2% of isolates demonstrating intermediate resistance (MIC = 0.1–1 mg/L) and 2.6% of isolates demonstrating complete resistance (MIC ⩾ 2 mg/L) in 1990–1991.[6,7] Resistant strains are found worldwide; areas with the highest prevalence are South Africa, Spain, France, Eastern Europe, Korea, Japan and the most southerly areas of South America.[8,9] In the USA, most reports of resistant pneumococci come from Alaska and the South, but resistance is increasing in other states and in Canada. A study of the prevalence of penicillin-resistant pneumococci in metropolitan Atlanta found that 25% of all invasive isolates and over 40% of isolates from children under 6 years of age were resistant. The transmission of penicillin-resistant *S. pneumoniae* is most common amongst children (in day-care centres), the elderly (in nursing homes) and in the hospital setting, in particular in intensive care units.[2]

Macrolide resistance has also been frequently observed in streptococci, significantly limiting the usefulness of this class of drugs for the treatment of pneumonia. The frequency of erythromycin resistance is higher in parts of Europe (27.5% of all pneumococci studied in France in 1992 were resistant to erythromycin) than in the USA, where erythromycin-resistance rates of 3.7 and 2.2% were reported in children aged 1–2 years and 3–4 years, respectively, between 1991 and 1992.[10,11] Importantly, penicillin-resistant strains are frequently cross-resistant to macrolides. On the contrary, strains with diminished susceptibility (MIC ⩽ 2 mg/L) can be successfully treated with increased doses of macrolides.[12] Macrolide-resistant pneumococci have, in general, extremely high MICs (>128 mg/L), which precludes any possibility of treatment with increased dosage. It is true that some of these cases have been treated with apparent success,[13] but the spontaneous cure rate of pneumococcal disease remains unexplained. The mechanism involved in highly macrolide-resistant strains is still debatable; if a constitutive 'MLS-type' phenotype appears as the primary option, many strains remain inducible (R. Leclerc, personal communication). Another group of pneumococcal strains have 'intermediate' susceptibility to macrolides, with erythromycin MICs between 4 and 16 mg/L. Some of these strains do not harbour *erm* genes, and an efflux mechanism is suspected, similar to that found in staphylococci.

In a recent analysis, Pallares *et al*. found no statistically significant difference in mortality rates in patients with pneumococcal pneumonia caused by penicillin-susceptible and -resistant strains.[13] These findings indicate that

high-dose penicillin remains effective against resistant strains, at least for pneumococcal strains with an MIC of penicillin of ⩽2 mg/L.[12]

Other streptococci

Although penicillin resistance is most commonly recognized in strains of *S. pneumoniae*, there is evidence of penicillin resistance emerging in viridans streptococci and β-haemolytic streptococci (including groups B, C and G).[14] In addition, the emergence of non-pneumococcal streptococci with resistance to macrolides and aminoglycosides is likely to affect significantly the management of streptococcal infections. Viridans streptococci (particularly *Streptococcus mitis*) have recently emerged as a common cause of bacteraemia in leucopenic patients receiving antibacterial prophylaxis.[15] No penicillin-resistance has hitherto been described among *S. pneumoniae* but a small percentage of strains have been observed with diminished susceptibility to some oral cephalosporins.

Erythromycin, gentamicin and tetracycline resistance in streptococci has also been reported in studies in the USA and South Africa.[16,17] In a Spanish study, 14.3% of isolates of *Streptococcus milleri* were resistant to erythromycin and 37.1% to tetracycline.[18] As in the case of *S. pneumoniae*, a group of viridans streptococci may show 'intermediate resistance' to macrolides, again suggesting a 'new' mechanism, probably related to efflux pumps.

Streptococci develop resistance to erythromycin and other macrolides, lincosamides and streptogramin B (MLS_B) via plasmid-mediated induction of an enzyme that methylates ribosomal RNA; as a result, erythromycin and related macrolides fail to bind and are inactivated.[19] However, this does not affect the susceptibility of these pathogens to streptogramin A, indicating that the streptogramin combination quinupristin/dalfopristin may be active against streptococci with MLS_B resistance.[14] This combination is more active against completely susceptible streptococci, and remains very active against high-level erythromycin-resistant strains.

Enterococci

Enterococcal infections have emerged as one of the most common nosocomial infections in the past decade.[20,21] They are an important cause of infection in organ transplant recipients and other seriously ill patients, and have become a common intestinal colonizer among hospitalized patients.[21] Their management poses a tremendous problem as members of this species, particularly *Enterococcus faecium*, are resistant to a large number of antimicrobial agents.[7,14]

The resistance of enterococci to β-lactams (penicillin and ampicillin), through production of β-lactamase and alterations of PBPs, was overcome in the past by combined treatment with aminoglycosides and β-lactams which had a synergistic bactericidal effect. However, the development of high-level resistance to aminoglycosides over the last 15 years, which has been reported in as many as 25% of enterococcal isolates, has led to the failure of this treatment regimen.[7,14]

Vancomycin, either alone or in combination regimens, replaced combined β-lactam/aminoglycoside therapy in this setting; however, the now widespread plasmid-mediated resistance to glycopeptides has significantly limited the use of this agent. In the USA, the incidence of nosocomial enterococci resistant to vancomycin reported to the National Nosocomial Infections Surveillance System of the Centers for Disease Control and Prevention increased from 0.3% in 1989 to 7.9% in 1993.[22] To date, up to 18% of all enterococcal isolates are vancomycin-resistant.[23] As vancomycin-resistant *E. faecium* are also commonly resistant to ampicillin and to high-levels of aminoglycosides they have caused great concern worldwide for the management of infections caused by these organisms.

Treatment options for patients infected with vancomycin-resistant enterococci are limited. Tetracyclines and fluoroquinolones, which show good activity *in vitro*, are the standard agents; however, many isolates are resistant to the clinically achievable serum concentrations of these drugs. Furthermore, fluoroquinolones are not at present recommended for use in children and adolescents.

As enterococci, staphylococci and streptococci are known to share genetic material by conjugation, there is the additional concern that vancomycin resistance in enterococci may be transferred to other Gram-positive pathogens, specifically MRSA. Fortunately this has not been reported to date in *S. aureus*.

Staphylococci

Staphylococcus aureus

The majority of *S. aureus* strains produce β-lactamase and thus are resistant to penicillin. Seventy to ninety per cent of isolates demonstrate resistance to the penicillins and aminopenicillins, and cross-resistance to oxacillin and methicillin has become widespread in most countries.[7,14] MRSA is a major nosocomial pathogen causing infections in hospitals and long-term care facilities throughout the world. The percentage of *S. aureus* isolates that are resistant to methicillin in different countries are shown in the Figure.[24] Infection with MRSA accounts for 12% of all bacteraemias, and the pathogen has been implicated in surgical wound infection (28%) and skin infections (21%).

These infections are difficult to treat, as MRSA are usually also resistant to other antibacterial agents including aminoglycosides, macrolides, lincosamides, tetracyclines, cephalosporins, carbapenems, β-lactamase inhibitor combinations, trimethoprim and sulphonamides. MRSA

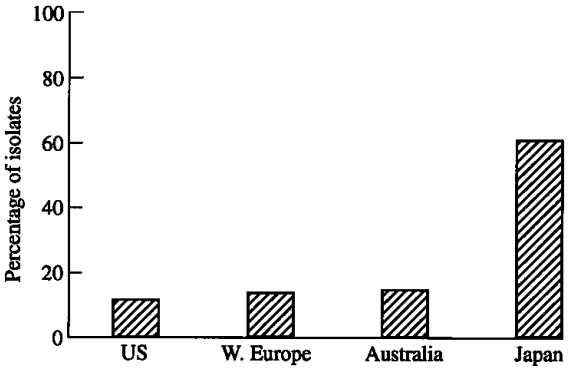

Figure. Prevalence of methicillin-resistant *S. aureus* in hospitals and long-term care facilities.[24]

were initially susceptible to the quinolones; however, resistance to this class of drugs has developed rapidly such that today more than 80% of MRSA isolates are quinolone-resistant.[25]

Vancomycin is currently used to treat MRSA infections, and resistance to this drug has not been reported in isolates of *S. aureus* to date; however, the potential for the transfer of plasmid-mediated resistance from enterococci is a great cause for concern.

Coagulase-negative staphylococci

The incidence of infections caused by coagulase-negative staphylococci has increased in recent years, particularly in intensive care patients in hospitals, immunosuppressed patients and in patients with prosthetic devices. These pathogens also frequently colonize the skin of patients and of hospital personnel.[26]

Resistance to methicillin and oxacillin is extremely common among coagulase-negative staphylococci, in particular *Staphylococcus epidermidis* and *Staphylococcus haemolyticus*.[27] In the USA, 65% of coagulase-negative staphylococcal blood isolates are resistant to oxacillin.[28] These pathogens have resistance patterns similar to that of *S. aureus*, and have also developed resistance to the quinolones. Unlike *S. aureus*, *S. haemolyticus* and *S. epidermidis* can be resistant to teicoplanin; reduced susceptibility to teicoplanin was found in 21% and 7% of these isolates, respectively, in a multicentre (n = 43) surveillance study conducted in the USA.[28] In addition, rare reports of vancomycin resistance in strains of *S. haemolyticus* provide a cause for concern.[17,28,29]

Other pathogens

Other pathogens that are becoming increasingly difficult to treat include the Gram-positive anaerobes *Peptostrep - tococcus* spp. and *Clostridium* spp. which have become resistant to penicillins and macrolides. Multiresistant strains of *Listeria* spp. and *Corynebacterium* spp. are also being isolated with increasing frequency.

Table II. *In-vitro* activity of quinupristin/dalfopristin against Gram-positive pathogens[32]

Phenotype (no. of strains)	Bacteriostatic activity (mg/L) MIC_{50}	MIC_{90}	MIC range
S. pneumoniae			
penicillin-S, erythromycin-S (32)	0.25	0.5	0.25–0.5
erythromycin-R (30)	0.5	1.0	0.125–2.0
penicillin-I, erythromycin-S (31)	0.5	0.5	0.25–1.0
penicillin-S (25)	0.5	1.0	0.25–1.0
penicillin-I (25)	0.5	1.0	0.5–1.0
penicillin-R (111)	0.25	0.5	0.03–1.0
Staphylococci			
methicillin-S *S. aureus* (40)	0.5	0.5	0.25–1.0
methicillin-R *S. aureus* (61)	0.5	1.0	0.5–1.0
methicillin-S *S. epidermidis, S. haemolyticus* (44)	0.5	0.5	0.25–1.0
methicillin-R *S. epidermidis, S. haemolyticus* (51)	0.5	0.5	0.25–1.0
erythromycin-S *S. epidermidis* (2)	–	–	0.13–0.25
erythromycin-R *S. epidermidis* (4)	–	–	0.13–0.25
other coagulase-negative staphylococci (22)	0.5	2.0	0.25–2.0
E. faecium			
vancomycin-S (118)	0.125	0.5	0.12–8.0
vancomycin-R, gentamicin-R (37)	–	0.5	0.06–1.0
vancomycin-R (35)	–	1.0	0.25–8.0

Abbreviations: S, susceptible; I, intermediate; R, resistant.

New agents currently under development

The above discussion indicates that new antibacterials with activity against multidrug-resistant Gram-positive pathogens are urgently needed for the treatment of severe multi-resistant hospital- and community-acquired infections (e.g. endocarditis caused by vancomycin-resistant *E. faecalis*, pneumococcal meningitis and otitis media).

Agents that are currently under rapid development and clinical investigation include the streptogramin combination quinupristin/dalfopristin, new ketolides, everninomicin derivatives (SCH 27899), oxazolidinones (U-100572, U-100766), several newer fluoroquinolones (clinafloxacin, DU 6859a, grepafloxacin, levofloxacin, sparfloxacin, trovafloxacin) and new glycopeptides.

There is much interest in the new semisynthetic injectable streptogramin quinupristin/dalfopristin.Streptogramins are a unique class of antibacterial agents in that the two structurally unrelated molecules act synergistically against bacteria. The majority of pathogens are susceptible and, importantly the possibility of selection of variants resistant to both components is reduced.[30]

Quinupristin/dalfopristin has shown high antibacterial activity *in vitro* and *in vivo* against most Gram-positive organisms including multiresistant strains (Table II) (for a review see Finch[31]). The drug has similar antibacterial activity *in vitro* against strains of *S. aureus* susceptible and resistant to methicillin, and against streptococci resistant to penicillin or erythromycin[32] and may thus prove useful for the management of several troublesome nosocomial infections. Most but not all strains of enterococci are susceptible to quinupristin/dalfopristin; importantly, in-vitro studies have demonstrated that strains of vancomycin-resistant *E. faecium* (VREF) are sensitive to quinupristin/dalfopristin.[32] Thus, the drug may be of particular value in the treatment of bacteraemia, endocarditis and intra-abdominal infections caused by VREF. In contrast, quinupristin/dalfopristin is much less active against *E. faecalis*.[33] The value of the drug against vancomycin-resistant *S. aureus* remains to be determined, if and when such strains arise.

Thus, while the results of clinical trials are awaited to determine the efficacy of this streptogramin in patients, preclinical findings suggest that quinupristin/dalfopristin is a promising agent for the treatment of multiresistant Gram-positive infections.

References

1. Schalberg, D. R. (1994). Resistant Gram-positive organisms. *Annals of Emergency Medicine* **3**, 462–4.

2. Hofmann, J., Cetron, M. S., Farley, M. M., Baughman, W. S., Facklam, R. R., Elliott, J. A. *et al.* (1995). The prevalence of drug-resistant *Streptococcus pneumoniae* in Atlanta. *New England Journal of Medicine* **333**, 481–6.

3. Appelbaum, P. C. (1996). Emerging resistance to antimicrobial agents in Gram-positive bacteria: pneumococci. *Drugs* **51**, *Suppl*., 1–5.

4. Friedland, I. R. & McCracken, G. H. (1994). Management of infections caused by antibiotic-resistant *Streptococcus pneumoniae*. *Drug Therapy* **331**, 377–82.

5. Spangler, S. K., Jacobs, M. R. & Appelbaum, P. C. (1994). In-vitro susceptibilities of 185 penicillin-susceptible and -resistant pneumococci to WY-49605 (SUN/SY 5335), a new oral penem, compared with those to penicillin G, amoxycillin–clavulanate, cefixime, cefaclor, cefpodoxime, cefuroxime, and cefdinir. *Antimicrobial Agents and Chemotherapy* **38**, 2902–40.

6. Spika, J. S., Facklam, R. R., Plikaytis, B. D., Oxtoby, M. J. & The Pneumococcal Surveillance Working Group. (1991). Antimicrobial resistance of *Streptococcus pneumoniae* in the United States. *Journal of Infectious Diseases* **163**, 1273–8.

7. Thornsberry, C. (1995). Trends in antimicrobial resistance among today's bacterial pathogens. *Pharmacotherapy* **15**, 3–5S.

8. Appelbaum, P. C. (1992). Antimicrobial resistance in *Streptococcus pneumoniae*: an overview. *Clinical Infectious Diseases* **15**, 77–83.

9. Baquero, F. (1995). Pneumococcal resistance to beta-lactam antibacterials: a global geographic overview. *Microbial Drug Resistance* **2**, 115–20.

10. Breiman, R. F., Butler, J. C., Tenover, F. C., Elliot, J. A. & Facklam, R. R. (1994). Emergence of drug resistant pneumococcal infection in the United States. *Journal of the American Medical Association* **271**, 1831–5.

11. Geslin, P., Fremaux, A., Sissia, G., Spicq, C. & Aberrance, S. (1994). Epidémiologie de la résistance aux antibiotiques de *Streptococcus pneumoniae* en France. Réseau national de surveillance (1984–1993). *Medecine et Maladies Infectieuses* **24**, 948–61.

12. Tomasz, A. (1995). The pneumococcus at the gates. *New England Journal of Medicine* **333**, 514–5.

13. Pallares, R., Linares, J., Vadillo, M., Cabellos, C., Manresa, F. & Viladrich, P. F. (1995). Resistance to penicillin and cephalosporin and mortality from severe pneumococcal pneumonia in Barcelona, Spain. *New England Journal of Medicine* **333**, 474–80.

14. Cormican, M. G. & Jones, R. N. (1996). Emerging resistance to antimicrobial agents in gram-positive bacteria: enterococci, staphylococcus and nonpneumococcal streptococci. *Drugs* **51**, *Suppl*., 6–12.

15. Bochud, P. Y., Eggiman, P., Calandra, T., Van Melle, G., Saghafit, L. & Francioli, P. (1994). Bacteraemia due to viridans streptococci in neutropenic patients with cancer: clinical spectrum and risk factors. *Clinical Infectious Diseases* **18**, 25–31.

16. Portgierter, E., Carmichael, M., Koornhoff, H. J. & Chalkley, L. J. (1992). *In vitro* and microbial susceptibility of viridans streptococci isolated from blood cultures. *European Journal of Clinical Microbiology and Infectious Diseases* **11**, 543–6.

17. Jones, R. N., Barry, A. L. & Gardiner, R. V. (1989). The prevalence of staphylococcal resistance to penicillinase-resistant penicillins. A retrospective and prospective trial of isolates from 40 medical centers. *Diagnostic Microbiology and Infectious Diseases* **12**, 383–94.

18. Gomez-Garces, J. L., Alos, J. I. & Cogollos, R. (1994). Bacteriologic characteristics and antimicrobial susceptibility of 70 clinically significant isolates of *Streptococcus milleri* group. *Diagnostic Microbiology and Infectious Diseases* **19**, 68–73.

19. Neu, H. C. (1992). The crisis in antibiotic resistance. *Science* **257**, 1064–72.

20. Morris, J. G., Shay, D. K., Hebden, J. N., McCarter, R. J., Perdue, B. E., Jarvis, W. *et al.* (1995). Enterococci resistant to multiple antimicrobial agents including vancomycin. *Annals of Internal Medicine* **123**, 250–9.

21. Schalberg, D. R., Culver, D. H. & Gaynes, R. P. (1991). Major trends in the microbial etiology of nosocomial infections. *American Journal of Medicine* **91**, *Suppl*., 72–5S.

22. Anon. (1993). Nosocomial enterococci resistant to vancomycin—United States 1989–1993. *MMWR Morbidity and Mortality Weekly Report* **42**, 597–9.

23. Rubinstein, E. & Keller, N. (1996). Future prospects and therapeutic potential of streptogramins. *Drugs* **51**, *Suppl*., 27–31.

24. Voss, A. & Doebbeling, B. N. (1995). The worldwide prevalence of methicillin-resistant *Staphylococcus aureus*. *International Journal of Antimicrobial Agents* **5**, 101–6.

25. Bauernfeind, A., Thornsberry, C. & Grassi, G. G. (1994). Panel discussion: quinolone resistance in Gram-positive bacteria. *Infectious Diseases in Clinical Practice* **3**, S133–5.

26. Archer, G. L. & Climo, M. W. (1994). Antimicrobial susceptibility of coagulase-negative staphylococci. *Antimicrobial Agents and Chemotherapy* **38**, 2231–7.

27. Swartz, M. N. (1994). Hospital acquired infections: diseases with increasingly limited therapies. *Proceedings of the National Academy of Sciences of the United States of America* **91**, 2420–7.

28. Jones, R. N., Kehberg, E. N., Erwin, M. E., Anderson, S. C. & The Fluoroquinolone Resistance Surveillance Group. (1994). Prevalence of important pathogens and antimicrobial activity of parenteral drugs at numerous medical centers in the United States. I. Study on the threat of emerging resistances: real or perceived? *Diagnostic Microbiology and Infectious Diseases* **19**, 203–15.

29. Schwalbe, R. S., Stapleton, J. T. & Gilligan, P. H. (1987). Emergence of vancomycin-resistance in coagulase-negative staphylococci. *New England Journal of Medicine* **316**, 927–31.

30. Pechère, J.-C. (1996). Streptogramins: a unique class of antibiotics. *Drugs* **51**, *Suppl*., 13–9.

31. Finch, R. G. (1996). Antibacterial activity of quinupristin/dalfopristin. Rationale for clinical use. *Drugs* **51**, *Suppl*., 31–37.

32. Pepper, K. & Bouanchaud, D. (1996). *In vitro* activity of quinupristin/dalfopristin (RP 59500) against Gram-positive pathogens: an update. *Expert Opinion on Investigational Drugs* **5**, 357–63.

33. Johnson, C. J., Slavoski, L., Schawartz, M., May, P., Pitsakis, P. G., Shur, A. L. *et al.* (1995). In vitro activity of RP 59500 (quinupristin/dalfopristin) against antibiotic-resistant strains of *Streptococcus pneumoniae* and enterococci. *Diagnostic Microbiology and Infectious Diseases* **21**, 169–73.