ORIGINAL ARTICLE

MRSA and MRSE: is there an answer?

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INTRODUCTION

In recent years, there has been a significant increase in nosocomial infections caused by *Staphylococcus aureus* and *Staphylococcus epidermidis*. In hospitals in the USA, the incidence of *S. aureus* infections doubled in the period 1980–89, while infections caused by coagulase-negative staphylococci (principally *S. epidermidis*) increased at least 4-fold [1]. Consequently, staphylococcal infections now account for a significant proportion of hospital-acquired infections, with *S. epidermidis* being the most common cause of bacteremia related to foreign bodies and indwelling medical devices [2]. Furthermore, coagulase-negative staphylococci are a known cause of bacterial endocarditis [3]. Nosocomial staphylococcal infections are associated with considerable morbidity and mortality, prolonging the duration of stay and increasing hospitalization costs. They are particularly significant in intensive care units (ICUs), where patients are at high risk of acquiring an infection due to the underlying disease(s) and/or exposure to invasive procedures [4,5]. The European Prevalence of Infection in Intensive Care Study (EPIC) conducted in 1992, found that 30% of all nosocomial infections were attributable to *S. aureus* and 19% to coagulase-negative staphylococci [4].

In the community, *S. aureus* is highly prevalent and is generally susceptible to a range of antibiotic classes including the β-lactams, whereas in the hospital setting, both *S. aureus* and *S. epidermidis* are frequently resistant to the β-lactam methicillin, and also to other antibiotics, and this represents a serious clinical problem [5]. This article reviews the background to methicillin-and multidrug-resistant staphylococci, examines the implications for infection control in hospitals, and discusses current and future treatment options for infections caused by these organisms.

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METHICILLIN RESISTANCE IN STAPHYLOCOCCI

Prevalence

The first clinical cases of methicillin-resistant *S. aureus* (MRSA) were identified in 1961 [6], only 2 years after methicillin became available for clinical use. Since then, the scale of the problem has increased dramatically, with the prevalence of MRSA reaching endemic proportions in some hospitals. However, considerable variations exist between countries and institutions. For example, in French ICUs in 1994–95, approximately 60% of *S. aureus* were methicillin resistant [7]. Comparable figures have been reported in some Belgian hospitals, while in others resistance rates are very low [8]. Other European countries, notably Scandinavia and The Netherlands, have an extremely low overall prevalence of MRSA infections [9,10]. Also, in the USA, approximately 25% of *S. aureus* strains are resistant to methicillin, whereas in Canada the prevalence rate is less than 5% [11].

As with *S. aureus*, methicillin-resistant *S. epidermidis* (MRSE) is a serious concern. Although there are marked geographic variations in MRSE prevalence, in some areas of Europe a high proportion (60%–70%) of *S. epidermidis* are methicillin resistant [12,13]. Comparable levels of methicillin resistance among coagulase-negative staphylococci have been reported in the USA [14].

Mechanisms of resistance

The mechanisms behind methicillin resistance are complex. β-Lactam antibiotics act by inhibiting the final stage of peptidoglycan biosynthesis in the bacterial cell wall by forming a stable complex with the penicillin-binding proteins (PBPs), which are vital for cell growth [15]. Methicillin resistance in staphylococci is frequently mediated by an additional PBP (PBP2a), which has a very low affinity for β-lactam agents [15]. The gene for PBP2a, mecA, is located in the mec determinant, which is only found in resistant bacterial strains. However, resistance levels can differ despite the presence of similar

amounts of PBP2a, suggesting that additional factors are involved in the phenotypic expression of methicillin resistance [15].

A number of genes called *fem* (factor essential for the expression of methicillin resistance) have now been identified in the *S. aureus* chromosome, of which *fem*AB appears to be the most important [15]. Inactivation of this gene totally restores methicillin susceptibility in MRSA strains. *fem*AB-like genes have also been identified in *S. epidermidis* [16].

In addition, genes encoding resistance to other antibiotics may be readily acquired by MRSA and so strains are frequently multidrug resistant [17].

SURVEILLANCE AND CONTROL OF DRUG-RESISTANT INFECTIONS

Selective pressure favoring drug-resistant bacterial strains has probably arisen from the widespread and sometimes inappropriate use of broad-spectrum antibiotics in medical and veterinary practice [18–20]. Antibiotic prophylaxis, high numbers of immunocompromised patients, and the increased use of invasive procedures and devices may also have had a role in this selection [11–18]. Inadequate infection control measures are also an important contributory factor.

In order to control the spread of drug-resistant strains within the hospital environment, education of healthcare workers and an effective infection control programme are essential. Infection control policies should take into account: (1) the prevalence and transmission rate of MRSA/MRSE at the institution (and any referring units); (2) modes of transmission specific to their institution; (3) reservoirs of infection (generally colonized or infected patients); (4) available resources; and (5) risk factors present in the patient population. Factors increasing the risk of nosocomial MRSA/MRSE infections in individual patients include prolonged hospital stay, exposure to broad-spectrum and/or multiple antibiotics and/or prolonged antibiotic therapy, surgical wounds, mechanical ventilation, central venous or urinary catheterization [4].

The effectiveness of infection containment policies for MRSA is well documented. For example, a study in a French ICU demonstrated a highly significant reduction in the rate of MRSA infection from 5.9 to 0.8 per 1000 patient-days after the implementation of rigorous hygiene measures [21]. The MRSA-carriage rate also fell significantly from 34% to 2% and the proportion of *S. aureus* strains resistant to methicillin fell from 71% to 11%. Further, at a hospital in the UK, the relaxation of a vigorous control program led to a dramatic rise in MRSA infections in the ensuing 18 months [22]. While data are not available for MRSE, containment policies should have a similarly dramatic effect on the transmission of this pathogen.

An infection containment strategy should include a surveillance system, rigorous handwashing, barrier precautions, isolation of colonized individuals, early detection and intervention, and stringent disinfection procedures [5–23]. Appropriate surveillance measures include a regular review of microbiologic culture and susceptibility results.

A characteristic feature of methicillin resistance is its heterogeneous nature, which can complicate conventional susceptibility testing, since resistance may vary according to the testing conditions used [15–24]. To facilitate the implementation of early control measures and help prevent further spread of resistant organisms, new molecular techniques, such as DNA probe hybridization, polymerase chain reaction, and pulsed-field gel electrophoresis, should be used to monitor for drug-resistant strains [24]. Patients at high risk of MRSA/MRSE and those with a history of MRSA/MRSE colonization or infection should be evaluated on admission to hospital. Patients at greatest risk of persistent MRSA carriage include those with skin lesions or sources of infection such as orthopaedic implants, catheters, or drains [25].

Additional infection control measures may be appropriate, in particular decolonization of staff and patients who are MRSA/MRSE carriers [23]. The implementation of hospital discharge policies for patients colonized with nosocomial strains of MRSA/MRSE may be advisable to prevent carriage of resistant organisms into the community. Mupirocin ointment is often used for the elimination of nasal MRSA, but the course of treatment should be limited in order to prevent the emergence of resistance [26].

In addition to infection control policies, the use of antibiotics should be rationalized to limit the dissemination of further drug resistance among MRSA/MRSE, as well as other bacterial strains [5]. A successful antibiotic control programme requires a multidisciplinary approach. Antibiotic policies often include a review of prescribing patterns, recommendations for first-line antibiotics, doses and duration of treatment, education of prescribing physicians, and appropriate microbiology testing and reporting [19]. For example, reports of susceptibility testing are restricted to recommended first-line drugs only, unless the isolate is resistant to these. Decisions on which antibiotics should be restricted should take into account the characteristics of the patient population and local resistance patterns, and the recommended first-line agents should be revised periodically. Options for restricting the use of certain antibiotics include rotating the agents recommended for empirical therapy and using combinations of drugs from different antibiotic classes [5].

ANTIBIOTIC THERAPY OF MRSA AND MRSE INFECTIONS

Antibiotic susceptibility testing in all potential cases of MRSA/MRSE infection is essential to determine the most appropriate therapy. Before the results of susceptibility tests are

available, decisions on empirical therapy need to be made, based on the local resistance pattern, the patient's response to any previous antibiotic therapy, the site of the infection, and the patient's underlying clinical condition. In addition to initiating appropriate antibiotic therapy, debridement, surgical removal of any foreign body, and/or drainage of purulent fluid/discharge (as appropriate) are essential elements of treatment.

MRSA/MRSE strains are frequently resistant to other antibiotic agents in clinical use, including other β-lactams, fluoroquinolones, aminoglycosides, rifamycins, and mupirocin. However, resistance rates to these antibiotics vary considerably between different centers and countries. Thus, while some institutions report very low rates of resistance to the rifamycin, rifampicin, among strains of MRSA [9–27], in others 60% of MRSA are rifampicin resistant [28]. Resistance to fluoroquinolones in MRSA can also be very high [9–28]. Similarly, 30%–100% of MRSA are resistant to clindamycin [10–13], while high rates of resistance to gentamicin [10–29] and fosfomycin [30] are also common. High levels of resistance to mupirocin in MRSA/MRSE have also been reported in some centers and this is associated with the increasing use of this agent as an adjunct to MRSA infection control measures [26]. Recent findings on resistance patterns among methicillin-resistant coagulase-negative staphylococci are similar. For example, in The Netherlands, 71% of coagulase-negative staphylococci strains resistant to methicillin were also resistant to gentamicin, 30% to clindamycin, and 37% to ciprofloxacin [10].

Thus, in centers where MRSA/MRSE have become multidrug resistant, therapeutic options are limited. Often, the glycopeptides (vancomycin and teicoplanin) are the only effective antibiotics remaining. This can present therapeutic difficulties when the infection is less accessible to drug penetration (e.g. infections of the central nervous system (CNS) or bone) or involves adherent bacteria (e.g. endocarditis or infections developing on prosthetic materials). In the latter situation, organisms that may be highly susceptible to the glycopeptides under standard in vitro laboratory conditions, are in fact tolerant in the biofilm environment, possibly due to a reduction in metabolic rate [18].

Current recommendations

For community-acquired staphylococcal infections, initial empirical therapy should comprise a combination of antibiotics until results of in vitro susceptibility tests are available; e.g. a β-lactam with an aminoglycoside for a skin or soft tissue infection and a glycopeptide combined with an aminoglycoside for patients with endocarditis. For a bone/joint infection, a fluoroquinolone should be combined with rifampicin, both of which exhibit good bone penetration, but carry a high risk of selection of resistance if given as a monotherapy [15]. Once the results of in vitro sensitivity testing are obtained, treatment regimens can be adjusted as appropriate.

With respect to nosocomial infections, the glycopeptides have become one of the last remaining options where MRSA/MRSE are suspected [31]. Patients with nosocomial pneumonia can receive a glycopeptide alone as empirical therapy; however, in sites where glycopeptide penetration is poor, such as in meningitis, a combination regimen should be used. A few clinical studies suggest that cefotaxime plus fosfomycin, rifampicin, or a quinolone could be used in addition to a glycopeptide while awaiting laboratory results [32]. In addition, on the basis of experimental studies, foreign body infections in which the adherent bacteria have reduced susceptibility to the glycopeptides could be treated with a triple combination regimen of vancomycin, rifampicin, and a quinolone [33].

As the glycopeptides are one of the few effective antibiotic classes for the treatment of infections caused by MRSA/MRSE, it is vitally important that they are used carefully to prevent the development of resistance. *Staphylococcus aureus* and *S. epidermidis* strains with reduced susceptibility to vancomycin have been isolated [34,35] and recently, vancomycin resistance in isolates of MRSA has been reported [36]. Resistance to teicoplanin has emerged in some coagulase-negative staphylococci [37] and in isolates of MRSA [38]. Fortunately, at present, the incidence of glycopeptide-resistant MRSA and MRSE strains in European hospitals is still extremely low [39]. However, the glycopeptides should not be prescribed for MRSA/MRSE infections that are responsive to other antibiotics.

When a glycopeptide is prescribed, blood levels should be monitored to ensure that effective concentrations are achieved. For vancomycin, trough levels should be at least 5–10 mg/L [15–23,40], while desirable trough levels for teicoplanin are at least 10 mg/L, although in endocarditis the trough should exceed 20 mg/L [23–40].

New therapeutic options

As a result of the poor extravascular penetration of the glycopeptides (limiting their utility in CNS, bone and joint infections) and the emergence of resistance to both vancomycin and teicoplanin in MRSA/MRSE, there is an urgent need for effective alternative antimicrobials for the treatment of infections caused by these pathogens. A number of antibiotics currently under clinical development may be suitable; these include the streptogramins, third-generation fluoroquinolones, glycylcyclines, oxazolidinones, new glycopeptides, and carbapenems.

The streptogramins have a unique mechanism of antibacterial action; they act by disrupting the translation of

mRNA into protein [41]. The injectable streptogramin, dalfopristin/quinupristin (RP59500, Synercid®; Rhone-Poulenc-Rorer), has shown considerable potential against multidrug resistant bacterial strains [41]. Dalfopristin/quinupristin is a combination of two molecules, dalfopristin, a group A streptogramin, and quinupristin, a group B streptogramin, in a 30/70 mixture. These two structurally unrelated components exhibit a synergistic effect on the 50S ribosome subunit [41]. The optimal dosing regimen has been defined as 7.5 mg/kg every 6–8 h, administered via a central line [42]. Dalfopristin/quinupristin shows rapid bactericidal activity against *Streptococcus pneumoniae,* although it may be less rapidly bactericidal against other Gram-positive cocci; minimal inhibitory concentrations (MIC) for *S. aureus* of 0.25–2 mg/L have been reported [41]. In vancomycin-susceptible organisms, the slow killing effect of dalfopristin/quinupristin is similar to that of vancomycin [11]. Dalfopristin/quinupristin may have a decreased activity against strains of MRSA that are constitutive producers of methylase, which mediates resistance to erythromycin [15]. The possibility of in vivo synergism of dalfopristin/quinupristin with β-lactams and vancomycin, particularly against staphylococci, has been suggested [42,43] but needs to be further investigated.

Several new third-generation fluoroquinolones, e.g. moxifloxacin and trovafloxacin, are active against Gram-positive cocci. However, ciprofloxacin-resistant MRSA/MRSE strains often exhibit decreased susceptibility to other fluoroquinolones, and it is unclear whether the newer fluoroquinolones will be useful against multidrug resistant strains of staphylococci [15].

The glycylcycline GAR936 exhibits increased activity against *S. aureus*, vancomycin-resistant enterococci and also penicillin-resistant *S. pneumoniae* [44]. To date, in vitro resistance to GAR936 has not been encountered, but the glycylcyclines do exhibit a slow rate of bacterial killing. The efficacy, tolerability and risk of selection of resistance of the glycylcyclines in vivo still needs to be established.

The oxazolidinone class of antibiotics is active not only against MRSA, but also against penicillin-resistant pneumococci and vancomycin-resistant enterococci [45], but have little activity against Gram-negative bacteria. Their mechanism of action is not yet fully understood, but they appear to be mainly bacteriostatic against staphylococci [46]. A number of oxazolidinones suitable for oral and intravenous administration are currently being investigated in phase II and III trials; of these, linezolid is at the most advanced stage of development.

New semisynthetic glycopeptides are also being investigated. LY333328, a glycopeptide derivative with a key N-alkylation substitution, is in phase I trials. In contrast to vancomycin, this antibiotic is highly bactericidal in vitro [47], although due to extensive protein binding its MIC increases markedly in the presence of albumin. The tolerability of the high doses of LY333328 required for therapeutic efficacy remains to be established.

Other new agents with therapeutic potential against MRSA/MRSE infections include the everninomicin SCH-27899 (Ziracin®; Schering Plough) [48], and some new carbapenems. Some agents of the latter class exhibit very low MICs against MRSA [49,50]. However, it is difficult to evaluate the in vivo efficacy of these agents in infections, such as endocarditis with left-sided localization or catheter-related infections, due to the lack of surrogate markers. Amoxicillin/clavulanic acid may also be of utility in MRSA/MRSE infections, although at present only experimental data in an endocarditis model are available; these show a comparable level of activity for amoxicillin/clavulanic acid to that of vancomycin against isolates of MRSA [51].

The emphasis of research, at present, is on investigating the molecular basis of methicillin resistance and finding novel antibacterial targets. Inactivation of the *fem* genes, which code for proteins (the FemAB proteins) necessary for bacterial growth, causes restoration of methicillin susceptibility in MRSA strains. It is hoped that these genes/proteins will prove to be useful targets for the antimicrobial agents of the future.

CONCLUSION

Multiply resistant strains of *S. aureus* and *S. epidermidis* represent a serious clinical problem, particularly in ICUs. The glycopeptides are one of the few antibiotic classes effective in the treatment of nosocomial infections caused by MRSA/MRSE, but due to their poor extravascular penetration and the emergence of resistance in both MRSA and MRSE, there is an urgent need to research other therapeutic options. In the meantime, the emergence and dissemination of resistance can be controlled by surveillance of the local bacterial population, early intervention, rigorous cross-infection control and judicious use of current antibacterial agents, based on bacterial identification and susceptibility testing data.

REFERENCES

1. Banerjee SN, Emori TG, Culver DH et al. Secular trends in nosocomial primary bloodstream infections in the United States, 1980–89. National Nosocomial Infections Surveillance System. *Am J Med* 1991; **91** (Suppl. 3B): S86–9.
2. Huebner J, Goldmann DA. Coagulase-negative staphylococci: role as pathogens. *Ann Rev Med* 1999; **50**: 223–36.
3. Caputo GM, Archer GL, Calderwood SB, DiNubile MJ, Karchmer AW. Native valve endocarditis due to coagulase-negative staphylococci. Clinical and microbiologic features. *Am J Med* 1987; **83**: 619–25.
4. Vincent JJL, Bihari DJ, Suter FM et al. The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) study. *JAMA* 1995; **274**: 639–44.

5. Weber DJ, Raasch R, Rutala WA. Nosocomial infections in the ICU. the growing importance of antibiotic-resistant pathogens. *Chest* 1999; **115** (Suppl. 3): S34–41.
6. Barber M. Methicillin-resistant staphylococci. *J Clin Path* 1961; **14**: 385–93.
7. Legras A, Malvy D, Quinioux AI et al. Nosocomial infections: prospective study of incidence in five French intensive care units. *Intensive Care Med* 1998; **24**: 1040–6.
8. Streulens MJ, Ronveaux O, Jans B, Mertens R. Methicillin-resistant *Staphylococcus aureus* epidemiology and control in Belgian hospitals. 1991–95. *Infect Control Hosp Epidemiol* 1996; **17**: 503–8.
9. Voss A, Milatovic D, Wallrauch-Schwarz C, Rosdahl VT, Braveny I. Methicillin-resistant *Staphylococcus aureus* in Europe. *Eur J Clin Microbiol Infect Dis* 1994; **13**: 50–5.
10. de Neeling AJ, Leeuwen van WJ, Schouls LM et al. Resistance of staphylococci in The Netherlands: surveillance by an electronic network during 1989–95. *J Antimicrob Chemotherapy* 1998; **41**: 93–101.
11. Jones RN, Low DE, Pfaller MA. Epidemiologic trends in nosocomial and community-acquired infections due to antibiotic-resistant Gram-positive bacteria: the role of streptogramins and other newer compounds. *Diagn Microbiol Infect Dis* 1999; **33**: 101–12.
12. Melo-Cristino J. Antimicrobial resistance in staphylococci and enterococci in 10 Portuguese hospitals in 1996 and 1997. POSGAR. Portuguese Study Group of Antimicrobial Resistance. *Micro Drug Resist* 1998; **4**: 319–24.
13. Schmitz FJ, Verhoef J, Fluit AC. Prevalence of resistance to MLS antibiotics in 20 European University hospitals participating in the European SENTRY surveillance programme. Sentry Participants Group. *J Antimicrob Chemother* 1999; **43**: 783–92.
14. Jones RN, Barry AL, Gardiner RV, Packer RR. The prevalence of staphylococcal resistance to penicillinase-resistant penicillins. A retrospective and prospective national surveillance trial of isolates from 40 medical centers. *Diagn Microbiol Infect* 1989; **12**: 385–94.
15. Chambers HF. Methicillin resistance in staphylococci: molecular and biochemical basis and clinical implications. *Clin Microbiol Rev* 1997; **10**: 781–91.
16. Alborn WE Jr, Hoskins J, Unal S et al. Cloning and characterization of *fem A* and *femB* from *Staphylococcus epidermidis*. *Gene* 1996; **180**: 177–8.
17. Kayser FH, Berger-Bachi B, Beck WD. Genetics of multiply-resistant *Staphylococcus aureus*. *J Hosp Infect* 1986; **7** (Suppl. A): 19–27.
18. Raad I, Alrahwan A, Rolston K. *Staphylococcus epidermidis*: emerging resistance and need for alternative agents. *Clin Infect Dis* 1998; **26**: 1182–7.
19. Duncan RA. Controlling use of antimicrobial agents. *Infect Control Hosp Epidemiol* 1997; **18**: 260–6.
20. Tenover FC, Hughes JM. The challenges of emerging infectious diseases. Development and spread of multiply-resistant bacterial pathogens. *JAMA* 1996; **275**: 300–4.
21. Cosseron-Zerbib M, Roque-Afonso AM, Naas T et al. A control programme for MRSA (methicillin-resistant *Staphylococcus aureus*) containment in a paediatric intensive acre unit: evaluation and impact on infections caused by other micro-organisms. *J Hosp Infect* 1998; **40**: 225–35.
22. Farrington M, Redpath C, Trundle C, Coomber S, Brown NM. Winning the battle but losing the war: methicillin-resistant *Staphylococcus aureus* (MRSA) infection at a teaching hospital. *QJM* 1998; **91**: 539–48.
23. Anonymous. Report of a combined working party of the British Society for Antimicrobial Chemotherapy, the Hospital Infection Society and the Infection Control Nurses Association. *J Hosp Infect* 1998; **39**: 253–90.
24. Pfaller MA, Cormican MG. Role of the microbiology laboratory in monitoring and identifying resistance: use of molecular biology. *New Horiz* 1996; **4**: 361–9.
25. Beaujean DJMA, Weersink AJL, Blok HEM, Frenay HME, Verhoef J. Determining risk factors for methicillin-resistant *Staphylococcus aureus* carriage after discharge from hospital. *J Hosp Infect* 1999; **42**: 213–18.
26. Cookson BD. The emergence of mupirocin resistance: a challenge to infection control and antibiotic prescribing practice. *J Antimicrob Chemother* 1998; **41**: 11–18.
27. Morgan M, Salmon R, Keppie N, Evans-Williams D, Hosein I, Looker DN. All Wales Surveillance of methicillin-resistant *Staphylococcus aureus* (MRSA): the first year's results. *J Hosp Infect* 1999; **4**: 173–9.
28. Gottlieb T, Mitchell D. The independent evolution of resistance to ciprofloxacin, rifampicin, and fusidic acid in methicillin-resistant *Staphylococcus aureus* in Australian teaching hospitals (1990–1995). Australian Group for Antimicrobial Resistance (AGAR). *J Antimicrob Chemother* 1998; **42**: 67–73.
29. Schneider C, Weindel M, Brade V. Frequency, clonal heterogeneity and antibiotic resistance of methicillin-resistant *Staphylococcus aureus* (MRSA) isolated in 1992–1994. *Zentralbl Bakteriol* 1996; **283**: 529–42.
30. Ferrara A, Dos Santos C, Cimbro M, Gialdroni Grassi G. Effect of different combinations of sparfloxacin, oxacillin, and fosfomycin against methicillin-resistant staphylococci. *Eur J Clin Microbiol Infect Dis* 1997; **16**: 535–7.
31. Michel M, Gutmann L. Methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci: therapeutic realities and possibilities. *Lancet* 1997; **349**: 1901–6.
32. Portier H, Tremeaux JC, Chavanet P, Gouyon JB, Duez JM, Kazmierczak A. Treatment of severe staphylococcal infections with cefotaxime and fosfomycin in combination. *J Antimicrob Chemother* 1984; **14** (Suppl. B): 277–84.
33. Schaad HJ, Chuard C, Vaudaux P, Waldvogel FA, Lew DP. Teicoplanin alone or combined with rifampin compared with vancomycin for prophylaxis and treatment of experimental foreign body infection by methicillin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother* 1994; **38**: 1703–10.
34. Sanyal D, Johnson AP, George RC, Cookson BD, Williams AJ. Peritonitis due to vancomycin-resistant *Staphylococcus epidermidis*. *Lancet* 1991; **337**: 54.
35. Garrett DO, Jochimsen E, Murfitt K et al. The emergence of decreased susceptibility to vancomycin in *Staphylococcus epidermidis*. *Infect Control Hosp Epidemiol* 1999; **20**: 167–70.
36. Kantzanou M, Tassios PT, Tseleni-Kotsovili A, Legakis NJ, Vatopoulos AC. Reduced susceptibility to vancomycin of nosocomial isolates of methicillin-resistant *Staphylococcus aureus*. *J Antimicrob Chemother* 1999; **43**: 729–31.
37. Sloos JH, van de Klundert JA, Dijkshoorn L, van Boven CP. Changing susceptibilities of coagulase-negative staphylococci to teicoplanin in a teaching hospital. *J Antimicrob Chemother* 1998; **42**: 787–91.
38. Mainardi JL, Shlaes DM, Goering RV, Shlaes JH, Acar JF, Goldstein FW. Decreased teicoplanin susceptibility of methicillin-resistant strains of *Staphylococcus aureus*. *J Infect Dis* 1995; **171**: 1646–50.
39. Gruneberg RN, Hryniewicz W. Clinical relevance of a European collaborative study on comparative susceptibility of gram-positive clinical isolates to teicoplanin and vancomycin. *Int J Antimicrob Agents* 1998; **10**: 271–7.
40. MacGowan AP. Pharmacodynamics, pharmacokinetics, and therapeutic drug monitoring of glycopeptides. *Ther Drug Monit* 1998; **20**: 473–7.
41. Barriere JC, Berthaud N, Beyer D, Dutka-Malen S, Paris JM, Desnottes JF. Recent developments in streptogramin research. *Curr Pharm Des* 1998; **4**: 155–80.
42. Bryson HM, Spencer CM. Quinupristin-dalfopristin. *Drugs* 1996; **52**: 406–15.
43. Lorian V, Fernandes F. Synergic activity of vancomycin-quinupristin/dalfopristin combination against *Enterococcus faecium*. *J Antimicrob Chemother* 1997; **39**: 63–6.
44. Petersen PJ, Jacobus NV, Weiss WJ, Sum PE, Testa RT. In vitro and in vivo antibacterial activities of a novel glycylcycline, the 9-t-butylglycylamido derivative of minocycline (GAR-936). *Antimicrob Agents Chemother* 1999; **43**: 738–44.

45. Patel R, Rouyse MS, Piper KE, Steckelberg JM. In vitro activity of linezolid against vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus* and penicillin-resistant *Streptococcus pneumoniae*. *Diagn Microbiol Infect Dis* 1999; **34**: 119–22.
46. Jorgensen JH, McElmeel ML, Trippy CW. In vitro activities of the oxazolidinone antibiotics U-100592 and U-100766 against *Staphylococcus aureus* and coagulase negative Staphylococcus species. *Antimicrob Agents Chemother* 1997; **41**: 465–7.
47. Mercier RC, Houlihan HH, Rybak MJ. Pharmacodynamic evaluation of a new glycopeptide, LY333328, and in vitro activity against *Staphylococcus aureus* and *Enterococcus faecium*. *Antimicrob Agents Chemother* 1997; **41**: 1307–12.
48. Urban C, Mariano N, Mosinka-Snipas K, Wadee C, Chahrour T, Rahal JJ. Comparative in-vitro activity of SCH 27899, a novel everninomicin, and vancomycin. *J Antimicrob Chemother* 1996; **37**: 361–4.
49. Malanoski G, Collins L, Eliopoulos CT, Moellering RC, Eliopoulos GM. Comparative in vitro activities of L-695,256, a novel carbapenem, against gram-positive bacteria. *Antimicrob Agents Chemother* 1995; **39**: 990–5.
50. Sumita Y, Nouda H, Kanazawa K, Fukasawa M. Antimicrobial activity of SM-17466, a novel carbapenem antibiotic with potent activity against methicillin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother* 1995; **39**: 910–16.
51. Moreillon P. Amoxycillin-clavulanate versus methicillin or isoxazolyl penicillins for treatment of *Staphylococcus aureus* infections. *J Antimicrob Chemother* 1995; **35**: 435–41.