UNIVERSITÀ
DEGLI STUDI
FIRENZE

FLORE

Repository istituzionale dell'Università degli Studi di Firenze

Antistaphylococcal (MSSA, MRSA, MSSE, MRSE) antibiotics

Questa è la Versione finale referata (Post print/Accepted manuscript) della seguente pubblicazione:

Original Citation:

Antistaphylococcal (MSSA, MRSA, MSSE, MRSE) antibiotics / F. Paradisi; G. Corti; D. Messeri. - In: THE MEDICAL CLINICS OF NORTH AMERICA. - ISSN 0025-7125. - STAMPA. - 85(2001), pp. 1-17.

Availability:

This version is available at: 2158/329747 since:

Terms of use:

Open Access

La pubblicazione è resa disponibile sotto le norme e i termini della licenza di deposito, secondo quanto stabilito dalla Policy per l'accesso aperto dell'Università degli Studi di Firenze (<https://www.sba.unifi.it/upload/policy-oa-2016-1.pdf>)

Publisher copyright claim:

(Article begins on next page)

optimal clinical outcomes while minimizing resistance potential problems and applying pharmacoeconomic considerations to antibiotic selection.

Infectious Disease Division
Winthrop-University Hospital
Mineola, NY 11501

BURKE A. CUNHA, MD
Guest Editor

ANTIBIOTIC THERAPY, PART II

0025-7125/01 \$15.00 + .00

ANTISTAPHYLOCOCCAL (MSSA, MRSA, MSSE, MRSE) ANTIBIOTICS

Franco Paradisi, MD, Giampaolo Corti, MD,
and Daniela Messeri, MD

Coagulase-positive (*Staphylococcus aureus*) and coagulase-negative staphylococci are gram-positive cocci appearing in clusters that are important causes of infection, primarily of the bloodstream, native and prosthetic cardiac valves, other implanted devices, and skin. Their progressively reduced susceptibility to penicillin, methicillin, and glycopeptides makes treatment of staphylococcal infections difficult. This article reviews the current status and the future perspectives for the therapy of infections caused by *S. aureus* and coagulase-negative staphylococci, such as *S. epidermidis*.

STAPHYLOCOCCUS AUREUS

S. aureus has been known as a bacterial agent of infection since 1882, when Ogston⁴⁰ clarified its role in sepsis and abscess formation. A list of community-acquired and hospital-acquired infections caused by *S. aureus* follows:

- Bacteremia and sepsis
- Endocarditis of native and prosthetic cardiac valve
- Surgical site infection
- Toxic shock and scalded skin syndromes
- Localized skin infections (folliculitis, furuncle, abscess, cellulitis, impetigo, pyoderma, hydradenitis, mastitis)

From the Clinic of Infectious Diseases, University of Florence School of Medicine, Florence, Italy

MEDICAL CLINICS OF NORTH AMERICA

VOLUME 85 • NUMBER 1 • JANUARY 2001

1

Bone and joint infections (osteomyelitis, septic arthritis)
 Food poisoning
 Bacterial meningitis
 Localized brain infections (epidural abscess, brain abscess, subdural empyema)
 Upper respiratory tract infections (otitis media, sinusitis)
 Lower respiratory tract infections (acute exacerbation of chronic bronchitis, pneumonia, pleural empyema)

Most of these infections occur in subjects with predisposing factors, primarily congenital or acquired (rheumatoid arthritis) chemotaxis defects, chronic granulomatous diseases, diabetes mellitus, or presence of foreign bodies.⁷⁵ At present, *S. aureus* is significant as a frequent and difficult agent of nosocomial infections. A report from the National Nosocomial Infections Surveillance System cited *S. aureus* as the most common cause of infection in U.S. hospitals, with an average 13% incidence. In particular, it was the first agent of surgical site infections and lower respiratory tract infections and the second cause of bloodstream infections and all other site infections excluding urinary tract infections (Fig. 1).³⁷

Epidemiology of β -Lactam Resistance

Originally, *S. aureus* was uniformly susceptible to penicillin, but soon after its introduction into clinical practice, penicillin resistance emerged as the result of the production of inactivating enzymes (i.e., β -lactamases).³¹ Currently, most *S. aureus* strains isolated from community-acquired lower respiratory tract infections are β -lactamase producers

Figure 1. Causes of nosocomial infections: prevalence rates (%) of staphylococci and other micro-organisms. SSI = surgical site infection, LRTI = lower respiratory tract infection, BSI = blood stream infection, UTI = urinary tract infection, CNS = coagulase-negative staphylococci. (Data from National Nosocomial Infections Surveillance (NNIS) Report, data summary, October 1986–April 1996, May 1996. Am J Infect Control 24:380, 1996.)

(approximately 80% in Europe and 90% in the United States) and resistant to penicillin and ampicillin.⁶⁰ These isolates usually remain susceptible to other β -lactams, such as penicillinase-resistant penicillins (nafcillin, oxacillin) penicillin- β -lactamase inhibitor combinations, and most cephalosporins.

In the 1950s, resistance of *S. aureus* to chloramphenicol, erythromycin, and the tetracyclines emerged,¹⁵ and in 1960, the first strains resistant to methicillin were isolated in London.²⁴ Methicillin resistance of staphylococci is mediated by the *mecA* gene, which encodes for penicillin-binding protein (PBP) 2a; PBP2a has low affinity for all β -lactams, conferring resistance not only to methicillin and other penicillins, but also to all β -lactams, including cephalosporins and carbapenems.⁸ Methicillin-resistant *S. aureus* (MRSA) frequently is cross-resistant to aminoglycosides, lincosamides, macrolides, tetracyclines, trimethoprim, and sulfonamides. By the end of the 1970s, MRSA isolates spread worldwide in hospitals and communities. In U.S. hospitals, the percentage of MRSA associated with nosocomial infections rose from 2.4% in 1975 to 29% in 1991.⁴¹ Similar results (29.3%) have been found in nosocomial bloodstream infections, with higher proportions of MRSA in the eastern United States (29.8% to 38.5%) than in the western United States (14.5% to 22.5%).¹² Sharp differences in MRSA prevalence rates between the United States (26.2%) and Canada (2.7%) have been noted as well.¹⁵

Intensive care units (ICUs) generally report the highest percentages of MRSA: a laboratory-based surveillance program conducted in the United States found a significantly higher prevalence of MRSA in ICU patients (35.2%) than in non-ICU inpatients (31.9%, $P < .01$).¹⁷ A European multicenter study reported an average rate of prevalence of 12.8%, ranging from less than 1% in Scandinavia to greater than 30% in Mediterranean countries (Spain, France, Italy). Distribution of MRSA strains was much higher (32.5%) in the ICUs, ranging from 0 in Holland to 52.9% in Austria and Italy.⁷³ The well-known European Prevalence of Infection in Intensive Care (EPIC) study reported an average rate of 59.6% and the highest prevalence (81%) found in Italy.⁷¹

MRSA is significantly less prevalent among outpatients (17.7%) than among inpatients (31.9% to 35.2%).¹⁷ Current trends in shortening hospital stays, performing outpatient surgery, and providing home parenteral therapies as well as the use of broad-spectrum antibiotics for community-acquired infections, injection drug abuse, and contact with MRSA-colonized subjects all increase the risk of the spread of hospital-acquired MRSA to the community.⁵³

Epidemiology of Reduced Susceptibility to Glycopeptides

S. aureus was fully susceptible to vancomycin and teicoplanin (the latter drug being available for clinical use in Europe and in other parts of the world but not in the United States). Transfer of resistance genes

from vancomycin-resistant enterococci (VRE) to *S. aureus* has been achieved in the laboratory, however.⁵⁹ The concern that vancomycin resistance might emerge and spread in *S. aureus* gained ground among microbiologists and clinicians in the early 1990s, and well-known reports on the decreased susceptibility of *S. aureus* to vancomycin exist. The first case of vancomycin-intermediate *S. aureus* (VISA) was reported in 1996 from Japan.⁷² Two VISA strains were isolated in 1997 in Michigan and New Jersey⁶⁰ and another one in the New York area in 1998.⁶¹ The first chronological appearance of a VISA strain probably occurred in France in November 1995, however, when it was isolated from a two-year-old girl with leukemia and MRSA bacteremia.⁶² These four strains shared the following factors: minimal inhibitory concentration (MIC) of vancomycin of 8 mg/L, presence of underlying disease, presence of indwelling medical devices, and previous therapy with vancomycin. MRSA strains with reduced susceptibility to teicoplanin (MIC $\geq$ 16 mg/L) have been isolated in Europe, the United States, and South America⁷³ so that the acronym GISA (glycopeptide-intermediate *S. aureus*) has been proposed as well.

Intermediate susceptibility to glycopeptides is difficult to detect with standard laboratory tests. Vancomycin susceptibility patterns of Michigan and New Jersey VISA strains varied according to the techniques performed: Broth microdilution methods found an 8 mg/L MIC of vancomycin (intermediate susceptibility), whereas disk-diffusion test reported 17- or 18-mm zone sizes (full susceptibility),⁶⁶ suggesting that the latter technique should not be used for testing staphylococci with vancomycin. A well-designed study verified that VISA isolates are best detected by nonautomated quantitative tests, such as the broth microdilution with the National Committee for Clinical Laboratory Standards (NCCLS) reference method, after a 24-hour incubation period, whereas the disk-diffusion test should not be used because it is less reliable; among commercial kits, MicroScan conventional panels (Dade Behring, West Sacramento, CA) and E-test (AB Biodisk North America, Piscataway, NJ) proved to be the most effective in detecting VISA strains.⁷⁰ The same study suggested that MRSA isolates for which the vancomycin MIC was greater than or equal to 4 mg/L should be considered to have reduced vancomycin susceptibility and should be carefully studied. In the United States, the percentage of MRSA strains with a vancomycin MIC of 4 mg/L increased from 0.2% in 1995 to 0.4% in 1997 for all isolates and from 0 to 0.4% for blood isolates.⁵⁶

The mechanism of reduced susceptibility to glycopeptides is still unclear, but it seems not to be due to the *van* genes present in enterococci.⁷⁰ Some researchers have found a hyperproduction of PBP2 that compete with vancomycin for binding to peptidoglycan precursors⁶⁶; other scientists have noted alteration in the structure of cell walls (thickening, hyperproduction of nonamated mucopeptides, reduced cross-linking of the peptidoglycan) resulting in reduced amounts of drug available at bacterial targets.^{18, 64} Elucidation of resistance mechanisms is of great importance because current efforts in drug development

are directed against the enterococcal mechanism of resistance to vancomycin.

Prevention and Control of Antibiotic-Resistant *Staphylococcus aureus* Infection

Measures to prevent and control spread of MRSA and GISA are crucial and include early isolation of patients, use of contact precautions (hand washing and use of gloves, gowns, and masks), ward closure, and screening of patients and health personnel for carriage.^{7, 74} Prudent use of antibiotics is mandatory above all, however, because it has been known for years that there is a causal association between antimicrobial usage and antimicrobial resistance.³⁵ Some authors have assumed that MRSA strains emerged and spread in hospitals after the use of prophylactic narrow-spectrum cephalosporins and use of therapeutic doses of third-generation cephalosporins.⁵⁶ As a result of new control strategies decreasing administration of cephalosporins in favor of piperacillin-tazobactam, the prevalence of MRSA isolates declined in a U.S. hospital from 35% to 23%.⁶⁵ After the emergence of VRE and GISA strains, the Centers for Disease Control and Prevention published new exhaustive guidelines, and a prudent use of vancomycin was cited as the major factor contributing to limited spread of these troublesome multiresistant bacteria.^{23, 52}

Antimicrobial Agents for Treatment of *Staphylococcus aureus* Infection

β -Lactams are the cornerstone for treatment of susceptible *S. aureus* infections. Vancomycin must be reserved only for patients with a history of β -lactam allergy because it appears to be a less effective antistaphylococcal drug than β -lactams.²⁹ Treatment failures with vancomycin have been observed in 10% to 20% of patients with endocarditis compared with 5% to 10% of β -lactams.⁸ In Europe and in other parts of the world, teicoplanin is available as well.

Penicillin remains the drug of choice for therapy of infections caused by penicillin-susceptible *S. aureus* strains. Severe infections must be treated intravenously with penicillin G (Table 1); addition of gentamicin is advisable for endocarditis to profit by the synergistic effect of the combination β -lactam-aminoglycoside.⁶¹ Further addition of rifampin to the combination of penicillin (or a glycopeptide in allergic subjects) and gentamicin has been advocated for treatment of prosthetic-valve endocarditis,⁷⁷ although the efficacy of rifampin as an adjunctive drug remains controversial. Patients with mild infections alternatively can be treated with less potent oral agents, such as penicillin V and others that are generally effective against penicillin-susceptible isolates (cotrimoxazole, lincosamides, macrolides, tetracyclines).

Table 1. ANTIBIOTIC THERAPY OF STAPHYLOCOCCAL INFECTIONS*

Susceptibility of Isolate	First Choice	Alternatives	Comments
Penicillin-susceptible	Severe infections: Penicillin G 4 million units every 4 h IV (24 million U/d in IV continuous infusion) Mild infections: Penicillin V 250 mg tid orally	Severe infections: Vancomycin 1 g bid IV Teicoplanin 3 mg/kg (mild infections), 6 mg/kg (severe infections), 12 mg/kg (endocarditis) bid for the first 2-5 d (loading dose), followed by 3-12 mg/kg qd IV Mild infections: Co-trimoxazole 960 mg (1 double-strength tablet) bid orally Doxycycline 100 mg bid orally Erythromycin 500 mg qid orally Clindamycin 300 mg qid orally	Addition of an aminoglycoside (gentamicin 80-120 mg tid IV) advisable for endocarditis and of rifampin (600 mg qd orally) for prosthetic-valve endocarditis
Penicillin-resistant, methicillin (oxacillin)-susceptible	Severe infections: Nafcillin or oxacillin 2 g every 4 h IV Cefazolin 2 g tid IV Mild infections: Amoxicillin-clavulanate 1 g bid or tid orally	See above	See above
Methicillin (oxacillin)-resistant	Vancomycin 1 g bid IV Teicoplanin 3 mg/kg (mild infections), 6 mg/kg (severe infections), 12 mg/kg (endocarditis) bid for the first 2-5 d (loading dose), followed by 3-12 mg/kg qd IV	Co-trimoxazole 60 mg/kg/d in 2-4 divided doses IV (960 mg bid orally) Minocycline (or doxycycline) 100 mg bid IV or orally Ciprofloxacin 400 mg bid IV (500 mg bid orally) Levofloxacin 500 mg qd IV or orally Quinupristin-dalfopristin 7.5 mg/kg bid or tid IV Linezolid 600 mg bid IV or orally Based on antimicrobial susceptibility pattern Investigational drugs (?): LY 333328, SCH 27899, glycylcyclines	See above
Oxacillin-resistant, with reduced susceptibility to vancomycin	Quinupristin-dalfopristin 7.5 mg/kg bid or tid IV Linezolid 600 mg bid IV or orally		

*Dosage must be adjusted in patients with altered renal function treated with aminoglycosides or glycopeptides (or both).

Penicillinase-resistant penicillins, such as nafcillin and oxacillin or, alternatively, narrow-spectrum cephalosporins, such as cefazolin, are indicated for infections caused by penicillin-resistant methicillin-susceptible *S. aureus* (MSSA) strains. As in the case of penicillin-susceptible isolates, glycopeptides and miscellaneous oral agents are alternatives in patients with allergy to β -lactams and mild infection.

The range of antimicrobials available for treatment of MRSA infections is more restricted. Glycopeptides are the drugs of choice, with similar *in vitro* and *in vivo* activity of vancomycin and teicoplanin,⁷⁸ although some European researchers have found a MIC of vancomycin (1 mg/L) significantly higher than that of teicoplanin (0.5 mg/L) against *S. aureus* isolates regardless of their susceptibility to methicillin.⁷⁹ In patients who do not respond initially to vancomycin, addition of rifampin is advisable because this combination has proved more effective.⁸

The problem arises in patients who cannot tolerate glycopeptides, although many alternative agents are, in theory, available.⁵¹ β -lactam- β -lactamase inhibitor combinations have been effective *in vitro* and in experimental endocarditis, but there is no human experience.¹⁶ Some serious infections have been treated successfully with co-trimoxazole, but studies on its efficacy against clinical MRSA isolates in Europe and the United States have reported resistance rates of 47% to 76% and 100%, respectively; similar results have been obtained with clindamycin (30% to 97% in Europe and 98% in the United States) and erythromycin (38% to 97% in Europe and 92% in the United States).^{73,74} Rifampin is a potent and bactericidal antistaphylococcal agent, but high-level resistant strains occur early *in vivo* if it is used alone so that rifampin must be used only in combination with another effective antistaphylococcal agent. Low-dose tetracyclines, such as doxycycline and minocycline, seem to be active *in vitro* and bactericidal for some isolates. Aminoglycoside-modifying enzymes produced by many MRSA strains generally make aminoglycosides not useful in this setting.^{8,11}

Fluoroquinolones initially were active against MRSA, but soon after their introduction into clinical practice resistance emerged and spread, primarily among *Pseudomonas aeruginosa* and MRSA.³⁸ The latter has become resistant to ciprofloxacin in 70% to 80% of cases in Europe and the United States,^{10,33} and it is cross-resistant to the other agents of the group.⁷⁴ Provided that a MRSA strain is susceptible to a fluoroquinolone, combination with rifampin to prevent emergence of resistance during therapy is desirable. Newer fluoroquinolones with enhanced activity against gram-positive cocci are now (or will soon be) available, and cinafloxacin appears to possess the best activity against ciprofloxacin-resistant strains (Table 2).²⁶ There is concern, however, that bacterial resistance can emerge early and spread widely with use of these molecules, as has occurred with former agents.

New enthusiasm has been generated by the development of potent antimicrobials primarily active against difficult gram-positive cocci, such as VRE, MRSA, and penicillin-resistant pneumococci: streptogramins (quinupristin-dalfopristin), oxazolidinones (linezolid), glycopeptides (LY

Table 2. COMPARATIVE IN VITRO ACTIVITIES (MIC₉₀ IN µg/L) OF NEWER FLUOROQUINOLONES AGAINST METHICILLIN-RESISTANT *S. AUREUS* BASED ON CIPROFLOXACIN SUSCEPTIBILITY

Agent	Ciprofloxacin-Susceptible Strains	Ciprofloxacin-Resistant Strains
Cinafloxacin	≤0.06	1
Moxifloxacin	≤0.06	2
Trovafloxacin	≤0.06	4
Grepafloxacin	≤0.06	32
Sparfloxacin	0.12	16
Levofloxacin	0.25	16
Ofloxacin	0.5	32
Ciprofloxacin	1	64

MIC₉₀ = Minimal inhibitory concentration that prevents growth of 90% of the strains.

Data from Jones ME, Vossen MR, Klooswijk M, et al: Comparative activities of cinafloxacin, grepafloxacin, levofloxacin, moxifloxacin, ofloxacin, sparfloxacin, and trovafloxacin and nonquinolones linezolid, quinupristin-dalfopristin, gentamicin, and vancomycin against clinical isolates of ciprofloxacin-resistant and -susceptible *Staphylococcus aureus* strains. *Antimicrob Agents Chemother* 43:421, 1999; with permission.

333328), evernimicin derivatives (SCH 27899), and newer semisynthetic tetracyclines (glycylcyclines). Quinupristin-dalfopristin is a new injectable streptogramin consisting of a synergistic and bactericidal combination of quinupristin and dalfopristin (two semisynthetic bacteriostatic derivatives of pristinomycin 1A and 1B, respectively, in a natural 30:70 ratio; it is active in vitro against MRSA, with MIC₉₀ of 0.25 to 2 mg/L⁶, and it has proved effective in the therapy of MRSA infections such as bacteremia, nosocomial pneumonia, and skin and soft tissue infection.⁴⁵

Other investigational drugs are in preclinical or clinical phase II-III evaluation. Oxazolidinones such as linezolid are synthetic bacteriostatic antimicrobials that are active in vitro against MRSA, although with higher MIC₉₀ (4 mg/L) than that of vancomycin.⁵⁵ Preliminary results from clinical trials indicate the good efficacy of linezolid in the treatment of bacteremias and skin and soft tissue infections caused by MRSA, with the favorable possibility of switch therapy from intravenous to oral administration.⁵ LY 333328 is a glycylpeptide antibiotic that is not only active (MIC, <0.25 to 2 mg/L), but also bactericidal (minimal bactericidal concentration, 1 to 2 mg/L) against *S. aureus*⁵⁹ and it appears to be bactericidal against GISA as well.²⁰ SCH 27899 is an oligosaccharide evernimicin antibiotic that is highly active against MRSA, with MIC₉₀ of 0.25 mg/L.²⁸ CL 329,998 and CL 331,002 are semisynthetic derivatives of minocycline and demethyldeoxytetracycline, which, respectively, are considerably more active than minocycline and slightly more effective than glycylpeptides against MRSA, with MIC₉₀ of 0.25 mg/L.⁶² The activity of a more recent derivative of minocycline, GAR-936, is 2 dilutions lower than that of CL 329,998 and CL 331,002 against MRSA, with MIC₉₀ of 0.5 mg/L.⁶⁴ Regarding treatment of GISA infections, no definite guidelines have been published until now. The first two U.S. isolates were susceptible to quinupristin-dalfopristin, tetracycline, chlorampheni-

col, and co-trimoxazole (one strain also to rifampin, and the infection was treated successfully with co-trimoxazole and rifampin),⁶⁶ whereas the infection in the Japanese patient responded to ampicillin-sulbactam plus atekacin (an aminoglycoside available in Japan,⁷² and the French patient was treated successfully with quinupristin-dalfopristin).⁴⁶ Antibiotic therapy of these difficult-to-treat infections must be guided by laboratory tests; however, it is possible that the new potent investigational drugs such as quinupristin-dalfopristin and linezolid could have a prominent role in this field.

STAPHYLOCOCCUS EPIDERMIDIS AND OTHER COAGULASE-NEGATIVE STAPHYLOCOCCI

Coagulase-negative staphylococci are natural inhabitants of the human skin. *S. epidermidis* is the most prevalent species, accounting for 65% to 90% of all staphylococci recovered, the second most frequent species being *S. hominis*. Other species are less frequent (*S. haemolyticus*, *S. warneri*), transient residents of the skin (*S. xylosus*, *S. simulans*, *S. cohnii*) or present in specific sites (*S. auricularis* in the ear canal, *S. capitis* on the head, *S. saprophyticus* on the genitourinary skin).¹

For many years, *S. epidermidis* and other coagulase-negative staphylococci isolated from the blood of hospitalized patients have been considered contaminants. It often is difficult to determine whether these organisms cause true bacteremia or they are only contaminants, however. Factors that have been shown to predict a true bacteremia are (1) resistance to at least six antimicrobials, (2) *S. epidermidis* species and biotype, (3) more than one positive blood culture, and (4) mean colony count of 33.2 per milliliter of blood as determined by quantitative blood cultures.⁷¹

In the United States, the incidence of coagulase-negative staphylococci in nosocomial bacteremia increased from 9% in 1980 to 27% in 1989,⁵⁷ and coagulase-negative staphylococci have been found to be the leading cause of nosocomial bloodstream infections (see Fig. 1).³⁷ The emergence of *S. epidermidis* as a major cause of nosocomial bacteremia is due to many factors, including (1) the widespread use of indwelling vascular access devices together with urinary, peritoneal, and ventricular indwelling devices in the management of a variety of life-threatening and chronic diseases; (2) the increasing use of broad-spectrum antibiotics, especially β-lactams, in the prevention and treatment of infections in hospitalized patients; and (3) the high proportion of neutropenic and otherwise immunocompromised patients in hospitals.⁴⁷ A list of community-acquired and hospital-acquired infections caused by *S. epidermidis* and other coagulase-negative staphylococci follows:

- Urinary tract infections
- Hospital-acquired (*S. epidermidis*)
- Female outpatients (*S. saprophyticus*)

Osteomyelitis
Sternal wound
Hematogenous
Endocarditis of the native valve
Bacteremia in immunosuppressed patients
Endophthalmitis after ocular surgery
Infections of indwelling foreign devices
Intravenous catheters
Hemodialysis shunt and grafts
Peritoneal dialysis catheters
Pacemaker wires and electrodes
Prosthetic joints
Vascular grafts
Prosthetic cardiac valves
Breast implants

Epidemiology of β -Lactam Resistance

Currently, β -lactamase-mediated resistance of coagulase-negative staphylococci to penicillin G (and consequently to all β -lactamase-susceptible penicillins) has reached rates of 70% to 90% in the United States and Europe.^{27,28} Resistance to methicillin is common among nosocomially acquired *S. epidermidis* isolates.³⁴ The prevalence of methicillin-resistant coagulase-negative staphylococci has increased rapidly over the last 3 decades because of the selective pressure of the increasing use of β -lactams. In the United States, the incidence of methicillin-resistant coagulase-negative staphylococci increased from 20% in 1980 to 60% in 1989,³⁷ 65% of coagulase-negative staphylococci blood isolates have been found to be oxacillin-resistant³⁷ but higher rates (80% to 85%) have been reported with *S. epidermidis*.² In Finland, the incidence of methicillin-resistant *S. epidermidis* (MRSE) increased from 28% in 1983 to 77% in 1994, simultaneously with an increasing use of penicillinase-stable β -lactams.³⁴ The EPIC study revealed a 70.1% rate of MRSE among ICU clinical isolates of *S. epidermidis*.³⁸ The mechanism of methicillin resistance of *S. epidermidis* is the same as *S. aureus*,³ and *van* genes typical of VRE have not been found in either species.²⁹

Epidemiology of Resistance to Other Antimicrobial Agents

Methicillin-resistant coagulase-negative staphylococci strains generally are cross-resistant to all β -lactams as well as to many other classes of antimicrobials, with wide differences linked to local variations in their use. Isolates from different geographic areas of the United States were shown to be 23% resistant to chloramphenicol; 35%, to tetracycline, 50%, to trimethoprim; 60%, to clindamycin; 61%, to gentamicin; and 75%, to

erythromycin.³ Figures of 31%, 39%, 60%, 30%, 71%, and 60% have been found in the Netherlands.¹¹

As in the case of *S. aureus*, fluoroquinolones initially were shown to be highly active against not only methicillin-susceptible *S. epidermidis* (MRSE), but also MRSE. Quinolone-resistant *S. epidermidis* strains emerged early in relation to the wide use of these antimicrobials in the community as well as in the hospital, however.³² For example, in Europe, more than 50% of methicillin-resistant coagulase-negative staphylococci are resistant to ciprofloxacin.³³ Among newer fluoroquinolones with enhanced activity against gram-positive cocci, clinafloxacin and moxifloxacin appear to possess the best activity, with MIC₉₀ of 0.06 to 1 mg/L.⁴

In contrast to *S. aureus*, teicoplanin is significantly less active than vancomycin against coagulase-negative staphylococci, in particular, *S. haemolyticus* and, to a lesser extent, *S. epidermidis*.³⁹ Reduced susceptibility to teicoplanin (MIC, 16 mg/L) was found in the United States in 21% and 7% of *S. haemolyticus* and *S. epidermidis* isolates, respectively.²⁷ More recently, vancomycin was uniformly active against methicillin-resistant coagulase-negative staphylococci, whereas full resistance to teicoplanin (MIC, ≥ 32 mg/L) was observed in 1.3% to 8.6% of strains worldwide.²⁵ The mechanism of glycopeptide resistance in *S. epidermidis* still is unknown, although resistance has been attributed to the thickening and irregularity of the cell wall or to the increased capacity of the cell wall to bind and sequester glycopeptides.⁷⁹ *S. epidermidis* organisms associated with device-related infections produce a slimy material, structurally defined as an exopolysaccharide (*slime*), which facilitates adherence of bacteria to smooth surfaces of prosthetic devices and forms a microbial biofilm.⁹ In a biofilm environment, highly vancomycin-susceptible organisms become tolerant to it when tested in vitro as dispersed bacteria. It has been reported that 134 *S. epidermidis* isolates from tips of indwelling vascular catheters were highly susceptible to vancomycin when tested in suspension, and only 5% were tolerant, whereas 100% of the strains were tolerant in the biofilm environment.³⁰ Tolerance of *S. epidermidis* embedded in biofilm has been attributed to poor penetration of glycopeptides through the biofilm matrix, suggesting that the slime itself serves as a barrier to antibiotic diffusion.¹⁴ Vascular catheter retention is known as a high-risk factor for recurrence of catheter-related bacteremia⁵⁰; these devices must be removed from patients with *S. epidermidis* bacteremia.

Antimicrobial Agents for Treatment of Staphylococcus epidermidis and Other Coagulase-Negative Staphylococcal Infections

Choice of drug therapy for infections resulting from coagulase-negative staphylococci depends on several factors, including the severity of the infection, underlying disease condition, infecting pathogen, and presence of resistant strains. Recommendations for treatment of *S. aureus*

infections summarized in Table 1 generally can be applied to the therapy of coagulase-negative staphylococcal infections. Because of the above-mentioned higher activity of vancomycin than that of teicoplanin, vancomycin is the drug of choice when a glycopeptide agent is required. Glycopeptide failure even with vancomycin in the treatment of nosocomial and device-related infections caused by MRSE and other coagulase-negative staphylococci has been described; in these cases, alternative agents, such as rifampin, minocycline, and others, must be considered.⁴⁷

Antistaphylococcal in vitro activity of rifampin is superior to that of many drugs, including vancomycin. When used in combination with glycopeptides, it improves their activity against *S. epidermidis* embedded in biofilm.⁴² The emergence of rifampin-resistant *S. epidermidis* has been reported, however, when rifampin is used not only in monotherapy but also in combination with nonlipophilic drugs active on the cell wall (β -lactams, glycopeptides).⁴⁸ *S. epidermidis* strains resistant to minocycline, the most active tetracycline against methicillin-resistant staphylococci, have been reported.⁴⁹ The combination of minocycline and rifampin is more effective than vancomycin alone or in combination with rifampin in preventing the colonization of catheter surfaces with slime-producing staphylococci.⁴⁹ In a multicenter randomized trial, minocycline and rifampin-coated central venous catheters were highly effective in preventing catheter-related bacteremia caused by *S. epidermidis* in high-risk patients.⁴⁸ Chloramphenicol, imipenem, and ciprofloxacin all have potential activity against methicillin-resistant staphylococci.^{13, 51} Because of increasing vancomycin resistance, however, there is now a clinical need for new types of antibiotics for the treatment of staphylococcal infections.

Quinupristin-dalfopristin has good bactericidal activity against MSSe and MRSE, with MIC₅₀ of 0.25 to 1 mg/L,⁶ and it has obtained satisfactory results in terms of clinical and microbiologic efficacy in preliminary studies on the treatment of bloodstream infections and skin and soft tissue infections resulting from MRSE and other coagulase-negative staphylococci.⁴⁵ Quinupristin-dalfopristin can be a therapeutic option in patients allergic to glycopeptides or receiving concomitant nephrotoxic drugs. The in vitro activity of oxazolidinones such as linezolid against MSSe and MRSE is comparable with that of vancomycin, with MIC₅₀ of 2 gm/L⁵⁵; it is possible that this new class of antimicrobials will be a valid alternative to glycopeptides in the treatment of systemic infections resulting from *S. epidermidis*. Preliminary results on the efficacy of linezolid in coagulase-negative staphylococcal infections of different sites show a positive clinical response in 10 of 11 patients.⁶⁰ As in the case of *S. aureus*, the glycopeptide antibiotic LY 333328 is not only active (MIC, 0.5 to 2 mg/L), but also bactericidal (minimal bactericidal concentration, 1 to 2 mg/L) against coagulase-negative staphylococci.¹⁹ The evernimonicin SCH 27899 is uniformly active against methicillin-susceptible and methicillin-resistant, coagulase-negative staphylococci with MIC₅₀ of 0.25 to 0.5 mg/L.²⁸ Glycylcyclines CL 329, 998 and CL 331,002 show a similar activity to those of minocycline and vancomycin

against methicillin-resistant coagulase-negative staphylococci, with MIC₅₀ of 2 mg/L.⁶² The activity of GAR-936 is 2 to 3 dilutions lower than that of CL 329,998 and CL 331,002 against MRSE, with MIC₅₀ of 1 mg/L.⁴⁴

SUMMARY

S. aureus and coagulase-negative staphylococci such as *S. epidermidis* are important causes of infection of the bloodstream, cardiac valves, implanted devices, and skin, with repercussions on mortality and increased economic costs. Treatment of staphylococcal infections is made difficult by the increasing emergence of resistance to β -lactams and other antimicrobials, including reduced susceptibility to glycopeptides. Penicillin must be used for infrequent penicillin-susceptible isolates, oxacillin and nafcillin are to be considered the major option for penicillin-resistant staphylococci, and glycopeptides are the drugs of choice for infections caused by methicillin-resistant strains. Co-trimoxazole, lincosamides, macrolides, tetracyclines, and fluoroquinolones are alternative agents, primarily in subjects allergic to β -lactams. Newly introduced or experimental drugs, such as streptogramins (quinupristin-dalfopristin), oxazolidinones (linezolid), carbapenems (LY 333328), evernimonicins (SCH 27899), and derivatives of tetracyclines (glycylcyclines), could be useful for therapy of infections caused by multiresistant staphylococci.

References

1. Archer GL: *Staphylococcus epidermidis* and other coagulase-negative staphylococci. In Mandell GL, Bennett JE, Dolin R (eds): *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, ed 4 (International Textbook of Infectious Diseases, vol 2). New York, Churchill Livingstone, 1995, p 1777
2. Archer GL, Climo MW: Antimicrobial susceptibility of coagulase-negative staphylococci. *Antimicrob Agents Chemother* 38:2231, 1994
3. Archer GL, Scott J: Conjugative transfer genes in staphylococcal isolates from the United States. *Antimicrob Agents Chemother* 35:2500, 1991
4. Bauerfeind A: Comparison of the antibacterial activities of the quinolones Bay 12-8039, gatifloxacin (AM 1155), trovafloxacin, cinafloxacin, levofloxacin and ciprofloxacin. *J Antimicrob Chemother* 40:639, 1997
5. Blumhagen MC, Zimmer GS, Hahn B, et al: Outcomes with linezolid (LZD) from an ongoing compassionate use (CU) trials of patients (Pts) with significant, resistant, gram-positive infections [abstr 1098]. In Abstracts of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, 1999, p 724
6. Bonachand DH: In-vitro and in-vivo antibacterial activity of quinupristin/dalfopristin. *J Antimicrob Chemother* 38(suppl A):15, 1997
7. Carbon C: Costs of treating infections caused by methicillin-resistant staphylococci and vancomycin-resistant enterococci. *J Antimicrob Chemother* 44 (topic A):31, 1999
8. Chambers HF: Methicillin resistance in staphylococci: Molecular and biochemical basis and clinical implications. *Clin Microbiol Rev* 10:781, 1997
9. Christensen GD, Simpson WA, Bisno AL, et al: Adherence of slime-producing strains of *Staphylococcus epidermidis* to smooth surfaces. *Infect Immun* 37:318, 1982

10. Coronado VG, Edwards JR, Culver DH, et al: Ciprofloxacin resistance among nosocomial *Pseudomonas aeruginosa* and *Staphylococcus aureus* in the United States. *Infect Control Hosp Epidemiol* 15:23, 1995
11. de Neeling AJ, van Leeuwen WJ, Schouls LM, et al: Resistance of staphylococci in the Netherlands: Surveillance by an electronic network during 1989-1995. *J Antimicrob Chemother* 41:33, 1998
12. Edmond MB, Wallace SE, McClish DK, et al: Nosocomial bloodstream infections in United States hospitals: A three-year analysis. *Clin Infect Dis* 29:229, 1999
13. Pagon JY, Maillet JM, Novara A: Hospital-acquired pneumonia: Methicillin resistance and intensive care unit admission. *Am J Med* 104(suppl 5A):17S, 1998
14. Fother BF, Kaplan MH, Clogston AG: *Staphylococcus epidermidis* extracted slime inhibits the antimicrobial action of glycopeptide antibiotics. *J Infect Dis* 161:37, 1990
15. Finland M: Changing patterns of resistance of certain common pathogenic bacteria to antimicrobial agents. *N Engl J Med* 252:570, 1955
16. Frase AP: Guidelines for the control of methicillin-resistant *Staphylococcus aureus*. *J Antimicrob Chemother* 42:287, 1998
17. Fridkin SK, Steward CD, Edwards JR, et al: Surveillance of antimicrobial use and antimicrobial resistance in United States hospitals: Project ICARE phase 2. *Clin Infect Dis* 29:245, 1999
18. Hanaki H, Labischinski H, Inaba Y, et al: Increase in glutamine-non-amidated muropeptides in the peptidoglycan of vancomycin-resistant *Staphylococcus aureus* strain Mu50. *J Antimicrob Chemother* 42:315, 1998
19. Harland S, Tabbs SE, Elliott TSJ: Evaluation of the in-vitro activity of the glycopeptide antibiotic LY333328 in comparison with vancomycin and teicoplanin. *J Antimicrob Chemother* 41:273, 1998
20. Hershberger E, Aeschlimann JR, Moldovan T, et al: Evaluation of bactericidal activities of LY 333328, vancomycin, teicoplanin, ampicillin-sulbactam, trovafloxacin, and RP59500 alone or in combination with rifampin or gentamicin against different strains of vancomycin-intermediate *Staphylococcus aureus* by time-kill curve methods. *Antimicrob Agents Chemother* 43:1717, 1999
21. Herwaldt LA, Geiss M, Kao C, et al: The positive predictive value of isolating coagulase negative staphylococci from blood cultures. *Clin Infect Dis* 22:14, 1996
22. Hiratsuka K, Hanaki H, Ito T, et al: Methicillin-resistant *Staphylococcus aureus* clinical strain with reduced vancomycin susceptibility. *J Antimicrob Chemother* 40:135, 1997
23. Interim guidelines for prevention and control of staphylococcal infection associated with reduced susceptibility to vancomycin. *MMWR Morb Mortal Wkly Rep* 46:626, 1997
24. Jevons MP: "Celbenin"-resistant staphylococci. *BMJ* 1:124, 1961
25. Jones ME, Jones RN, Sader H, et al: Current susceptibilities of staphylococci to glycopeptides determined as part of an international resistance surveillance programme. *J Antimicrob Chemother* 42:119, 1998
26. Jones ME, Vissen MR, Klooswijk M, et al: Comparative activities of cinafloxacin, grepafloxacin, levofloxacin, moxifloxacin, ofloxacin, sparfloxacin, and trovafloxacin and nonquinolones linezolid, quinupristin-dalfopristin, gentamicin, and vancomycin against clinical isolates of ciprofloxacin-resistant and -susceptible *Staphylococcus aureus* strains. *Antimicrob Agents Chemother* 43:421, 1999
27. Jones RN, Kohnberg EN, Erwin ME, et al: 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? *Diagn Microbiol Infect Dis* 19(suppl):203, 1994
28. Jones RN, Marshall SA, Erwin ME, et al: Antimicrobial activity and spectrum of SCH27899 (Zitracin) tested against gram-positive species including recommendations for routine susceptibility testing methods and quality control. *Diagn Microbiol Infect Dis* 34:103, 1999
29. Karchner AW: *Staphylococcus aureus* and vancomycin: The sequel. *Ann Intern Med* 115:739, 1991
30. Khairat N, Yassen M, Wilson K: Tolerance of *Staphylococcus epidermidis* grown from indwelling vascular catheters to antimicrobial agents. *J Ind Microbiol* 15:148, 1995

31. Kirby WM: Extraction of a highly potent penicillin inactivator from penicillin-resistant staphylococci. *Science* 99:452, 1944
32. Kotilainen J, Nikoskelainen J, Huovinen P: Emergence of ciprofloxacin resistant coagulase-negative staphylococcal skin flora in immunocompromised patients receiving ciprofloxacin. *J Infect Dis* 161:141, 1990
33. Kresken M, Hahner D, Mittermayer H, et al: Prevalence of fluoroquinolone resistance in Europe. *Infection* 22(suppl 2):S90, 1994
34. Lyytikäinen O, Vaara M, Järvinen E, et al: Increasing resistance among *Staphylococcus epidermidis* isolates in a large teaching hospital over a 12 year period. *Eur J Clin Microbiol Infect Dis* 15:133, 1996
35. McGowan JE Jr: Antimicrobial resistance in hospital organisms and its relation to antibiotic use. *Rev Infect Dis* 5:1033, 1983
36. Moreira B, Boyle-Vavra S, deJonge BL, et al: Increased production of penicillin-binding protein 2, increased detection of other penicillin-binding proteins, and decreased coagulase activity associated with glycopeptide resistance in *Staphylococcus aureus*. *Antimicrob Agents Chemother* 41:1788, 1997
37. National Nosocomial Infection Surveillance (NNIS) Report: Data summary from October 1986-April 1996, issued May 1996. *Am J Infect Control* 24:380, 1996
38. Neu HC: Bacterial resistance to fluoroquinolones. *Rev Infect Dis* 10(suppl 1):S57, 1988
39. Noble WC, Virani Z, Cree RCA: Co-transfer of vancomycin and other resistance genes from *Enterococcus faecalis* NCTC 12201 to *Staphylococcus aureus*. *FEMS Microbiol Lett* 93:195, 1992
40. Ogston A: Micrococci poisoning. *J Anat* 17:24, 1882
41. Panillo AL, Culver DH, Gaynes RP, et al: Methicillin-resistant *Staphylococcus aureus* in U.S. hospitals, 1975-1991. *Infect Control Hosp Epidemiol* 13:582, 1992
42. Pascual A, Ramirez de Arrellano E, Perez EJ: Activity of glycopeptides in combination with amikacin or rifampin against *Staphylococcus epidermidis* biofilms or plastic catheters. *Eur J Clin Microbiol Infect Dis* 13:515, 1994
43. Pechère JC: Current and future management of infections due to methicillin-resistant staphylococci: The role of quinupristin/dalfopristin. *J Antimicrob Chemother* 44(suppl A):11, 1999
44. Petersen PJ, Jacobus NV, Weiss WJ, et al: In vitro and in vivo antibacterial activities of a novel glycolylglycine, the 9- α -butyryl-glycylamido derivative of minocycline (GAR-936). *Antimicrob Agents Chemother* 43:738, 1999
45. Pfaller MA, Jones RN, Doern GV, et al: Bacterial pathogens isolated from patients with bloodstream infections: frequencies of occurrence and antimicrobial susceptibility patterns from the SENTRY Antimicrobial Surveillance Program (United States and Canada, 1997). *Antimicrob Agents Chemother* 42:1762, 1998
46. Ploy MC, Grélaud C, Martin C, et al: First clinical isolate of vancomycin-intermediate *Staphylococcus aureus* in a French hospital. *Lancet* 351:1212, 1998
47. Raad I, Alatravan A, Rolston K: *Staphylococcus epidermidis*: Emerging resistance and need for alternative agents. *Clin Infect Dis* 26:1182, 1998
48. Raad I, Darouiche R, Dupuis J, et al: Central venous catheters coated with minocycline and rifampin for the prevention of catheter-related colonization and bloodstream infection: A randomized, double-blind trial. *Ann Intern Med* 127:267, 1997
49. Raad I, Darouiche R, Hachem R, et al: Antibiotics and prevention of microbial colonization of catheters. *Antimicrob Agents Chemother* 39:2397, 1995
50. Raad I, Davis S, Khan A, et al: Impact of central venous catheter removal on the recurrence of catheter-related coagulase-negative staphylococcal bacteremia. *Infect Control Hosp Epidemiol* 13:215, 1992
51. Rahman M: Alternatives to vancomycin in treating methicillin-resistant *Staphylococcus aureus* infections. *J Antimicrob Chemother* 41:325, 1998
52. Recommendations for preventing the spread of vancomycin resistance: Recommendations of the Hospital Infection Control Practices Advisory Committee (HICPAC). *MMWR Morb Mortal Wkly Rep* 44 (RR-12):1, 1995
53. Rosenberg J: Methicillin-resistant *Staphylococcus aureus* (MRSA) in the community: Who's watching? *Lancet* 346:132, 1995

54. Rupp ME, Archer GL: Coagulase negative staphylococci: Pathogens associated with medical progress. *Clin Infect Dis* 19:231, 1994
55. Rybak MJ, Cappulety DM, Moldovan T, et al: Comparative in vitro activities and post-antibiotic effects of the oxazolidinone compounds operezolid (PNU-100592) and linezolid (PNU-100766) versus vancomycin against *Staphylococcus aureus*, coagulase-negative staphylococci, *Enterococcus faecalis* and *Enterococcus faecium*. *Antimicrob Agents Chemother* 42:721, 1998
56. Sahm DF, Marsilio MK, Piazza G: Antimicrobial resistance in key bloodstream bacterial isolates: Electronic surveillance with the Surveillance Network Database—USA. *Clin Infect Dis* 29:259, 1999
57. Schnaberg DR, Culver DH, Gaynes RP: Major trends in the microbial etiology of nosocomial infection. *Am J Med* 91(suppl 3B):72S, 1991
58. Schentag JJ, Hyatt JM, Carr JR, et al: Genes of methicillin-resistant *Staphylococcus aureus* (MRSA), how treatment of MRSA infections has selected for vancomycin-resistant *Enterococcus faecium*, and the importance of antibiotic management and infection control. *Clin Infect Dis* 26:1204, 1998
59. Schito GC, Auckenthaler R, Marchese A, et al: European survey of glycopeptide susceptibility in *Staphylococcus* spp. *Clin Microbiol Infect* 5:547, 1999
60. Schito GC, Debbia EA, Tesce A, and the Alexander Project Collaborative Group: Susceptibility of respiratory strains of *Staphylococcus aureus* to fifteen antibiotics: Results of a collaborative surveillance study (1992-1993). *J Antimicrob Chemother* 36(suppl A):97, 1996
61. Shanson DC: New guidelines for the antibiotic treatment of streptococcal, enterococcal and staphylococcal endocarditis. *J Antimicrob Chemother* 42:292, 1998
62. Shonken D, Handwerker S, Muldvan D: Comparative in-vitro activities of RP59500 (quinupristin/dalfopristin), CL 329 998, CL331 002, trovafloxacin, dalfloxacin, teicoplanin and vancomycin against gram-positive bacteria. *J Antimicrob Chemother* 39:405, 1997
63. Sieradzki K, Roberts RB, Haber SW, et al: The development of vancomycin resistance in a patient with methicillin-resistant *Staphylococcus aureus* infection. *N Engl J Med* 340:517, 1999
64. Sieradzki K, Tomasz A: Inhibition of cell wall turnover and autolysis by vancomycin in a highly-vancomycin-resistant mutant of *Staphylococcus aureus*. *J Bacteriol* 179:2557, 1997
65. Smith DW: Decreased antimicrobial resistance after changes in antibiotic use. *Pharmacotherapy* 19:129S, 1999
66. Smith TL, Pearson ML, Wilcox KR, et al: Emergence of vancomycin resistance in *Staphylococcus aureus*. *N Engl J Med* 340:493, 1999
67. Speer BS, Shoemaker NB, Salysers AA: Bacterial resistance to tetracycline: Mechanisms, transfer, and clinical significance. *Clin Microbiol Rev* 5:387, 1992
68. Spencer RC: Predominant pathogens found in the European Prevalence of Infection in Intensive Care study. *Eur J Clin Microbiol Infect Dis* 15:281, 1996
69. Stone J: Clinical experience with linezolid in a community hospital setting. [abstr 40.007]. In Abstracts of the 8th International Congress on Infectious Diseases, Boston, 1998, p 120
70. Tenover FC, Lancaster MV, Hill BC, et al: Characterization of staphylococci with reduced susceptibilities to vancomycin and other glycopeptides. *J Clin Microbiol* 36:1020, 1998
71. Vincent JL, Bihari DJ, Suter PM, et al: The prevalence of nosocomial infection in intensive care unit in Europe: Results of the European Prevalence of Infection in Intensive Care (EPIC) study. *JAMA* 274:639, 1995
72. Voss A, Kresken M: Antibiotic resistance in staphylococci in Europe. *Chemotherapy* 42(suppl 2):13, 1996
73. Voss A, Milatovic D, Wallrauch-Schwarz C, et al: Methicillin-resistant *Staphylococcus aureus* in Europe. *Eur J Clin Microbiol Infect Dis* 13:50, 1994
74. Wadsworth SJ, Kim K-H, Satsichandran V, et al: Development of new antibiotic resistance in methicillin-resistant but not methicillin-susceptible *Staphylococcus aureus*. *J Antimicrob Chemother* 30:821, 1992

75. Waldvogel FA: *Staphylococcus aureus* (including toxic shock syndrome). In Mandell GL, Bennett JE, Dolin R (eds): *Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases*, ed 4 (International textbook of Infectious Diseases, vol 2). New York, Churchill Livingstone, 1995, p 1754
76. Wenzel RP, Edmond MB: Vancomycin-resistant *Staphylococcus aureus*: Infection control considerations. *Clin Infect Dis* 27:245, 1998
77. Wilson WR, Karchner AW, Dajani AS, et al: Antibiotic treatment of adults with infective endocarditis due to streptococci, enterococci, staphylococci, and HACEK microorganisms. *JAMA* 274:1706, 1995
78. Wood MJ: The comparative efficacy and safety of teicoplanin and vancomycin. *J Antimicrob Chemother* 37:209, 1996
79. Woodford N, Johnson AP, Morrison D, et al: Current perspectives on glycopeptide resistance. *Clin Microbiol Rev* 8:585, 1995

Address reprint requests to
 Franco Paradisi, MD
 Clinic of Infectious Diseases
 University of Florence School of Medicine
 Careggi Hospital
 Viale G.B. Morgagni 85
 I-50134 Florence, Italy
 e-mail: infdis@unifi.it