Antistaphylococcal (MSSA, MRSA, MSSE, MRSE) antibiotics

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

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ANTISTAPHYLOCOCCAL (MSSA, MRSA, MSSE, MRSE) ANTIBIOTICS

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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 Ogston[40] 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)

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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

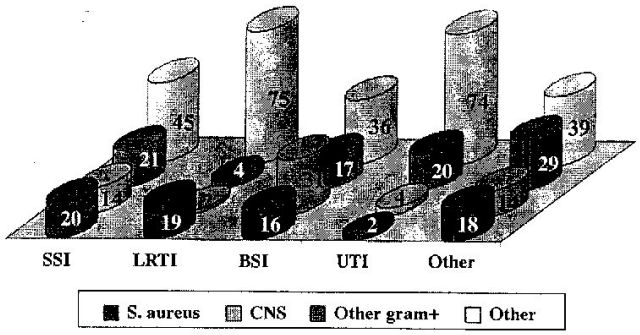

Figure 1. Causes of nosocomial infections: prevalence rates (%) of staphylococci and other micro-organisms. SSI = surgical site infection, LRTI = lower respiratory tract infection, BSI = blood stream infection, UTI = urinary tract infection, CNS = coagulase-negative staphylococci. (*Data from* National 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.[45]

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.[39] 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.[22] Two VISA strains were isolated in 1997 in Michigan and New Jersey[66] and another one in the New York area in 1998.[63] The first chronologic 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.[46] 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 America[25] 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 in 1995 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 PBPs that compete with vancomycin for binding to peptidoglycan precursors[36]; other scientists have noted alteration in the structure of cell walls (thickening, hyperproduction of nonamidated muropeptides, 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, 76] 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.[58] 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	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	Based on antimicrobial susceptibility pattern Investigational drugs (?): LY 333328, SCH 27899, glycylcyclines	

*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.[59] 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-dosage 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 clinafloxacin 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 (MIC_{90} IN mg/L) OF NEWER FLUOROQUINOLONES AGAINST METHICILLIN-RESISTANT *S. AUREUS* BASED ON CIPROFLOXACIN SUSCEPTIBILITY

Agent	Ciprofloxacin-Susceptible Strains	Ciprofloxacin-Resistant Strains
Clinafloxacin	≤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

MIC_{90} = Minimal inhibitory concentration that prevents growth of 90% of the strains.
Data from Jones ME, Vissen MR, Klootwijk M, et al: Comparative activities of clinafloxacin, 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), everninomicin derivatives (SCH 27899), and newer semisynthetic tetracyclines (glycylcylines). Quinupristin-dalfopristin is a new injectable streptogramin consisting of a synergistic and bactericidal combination of quinupristin and dalfopristin (two semisynthetic bacteriostatic derivatives of pristinomycin IA and IIA, respectively, in a natural 30:70 ratio; it is active in vitro against MRSA, with MIC_{90} of 0.25 to 2 mg/L[6], and it has proved effective in the therapy of MRSA infections such as bacteremia, nosocomial pneumonia, and skin and soft tissue infection.[43]

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 MIC_{90} (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 glycopeptide 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*,[19] and it appears to be bactericidal against GISA as well.[20] SCH 27899 is an oligosaccharide everninomicin antibiotic that is highly active against MRSA, with MIC_{90} 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 glycopeptides against MRSA, with MIC_{90} 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 MIC_{90} of 0.5 mg/L.[44] 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, chloramphenicol, 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 arbekacin (an aminoglycoside available in Japan,[22] 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. auricolaris* in the ear canal, *S. capitis* on the head, *S. saprophyticus* on the genitourinary skin).[1]

For many years, *S. epidermidis* and other coagulose-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.[21]

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, 72] Resistance to methicillin is common among nosocomially acquired *S. epidermidis* isolates.[54] 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,[57] 65% of coagulase-negative staphylococci blood isolates have been found to be oxacillin-resistant,[27] 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*.[68] The mechanism of methicillin resistance of *S. epidermidis* is the same as *S. aureus*,[8] and *van* genes typical of VRE have not been found in either species.[70]

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* (MSSE), 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 MIC_{90} 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*.[59] 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 bacteremia[50]; 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).[47] *S. epidermidis* strains resistant to minocycline, the most active tetracycline against methicillin-resistant staphylococci, have been reported.[67] 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 $MICs_{90}$ 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.[43] 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 MIC_{90} of 2 gm/L[55]; 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.[69] 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 everninomicin SCH 27899 is uniformly active against methicillin-susceptible and methicillin-resistant, coagulase-negative staphylococci with MIC_{90} 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 MIC_{90} 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 MIC_{90} 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), everninomicins (SCH 27899), and derivatives of tetracyclines (glycylcyclines), could be useful for therapy of infections caused by multiresistant staphylococci.

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