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MINIREVIEW

Antimicrobial Susceptibility of Coagulase-Negative Staphylococci

GORDON L. ARCHER[1,2]* AND MICHAEL W. CLIMO[1]

Departments of Medicine[1] and Microbiology/Immunology,[2] Division of Infectious Diseases, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia

INTRODUCTION

Coagulase-negative staphylococci (CoNS) are increasing in importance as causes of hospital-acquired infections, particularly nosocomial bacteremias (64). The National Nosocomial Infection Survey (NNIS) found that from 1980 to 1989, the incidence of CoNS as a cause of nosocomial bacteremias increased from 9 to 27% to become the single most common cause of these infections (64). Furthermore, NNIS data revealed that during this same period the proportion of nosocomial CoNS resistant to methicillin, oxacillin, or nafcillin increased from 20 to 60%. Most of these methicillin-resistant CoNS were also resistant to multiple additional antimicrobial agents. Thus, there is an association between the dramatic increase in CoNS as a cause of nosocomial bacteremias and the resistance of these pathogens to antimicrobial agents.

Multiresistant CoNS also commonly colonize the skin of hospitalized patients and hospital personnel (3). Widespread skin colonization serves as a potential reservoir for multiresistant isolates that can cause infections, particularly infections of indwelling intravascular devices. In addition, these colonizing isolates serve as a reservoir for antibiotic resistance genes that can transfer among CoNS and be acquired by *Staphylococcus aureus* (7, 31, 57).

This review article will summarize the available data on the susceptibility of CoNS to individual antimicrobial agents. Much of the available susceptibility data include neither the source nor the species of study isolates. However, the majority of isolates are *S. epidermidis*, methicillin-resistant isolates are most often nosocomial, and most isolates are from specimens processed in the clinical microbiology laboratory. Thus the susceptibility data summarized are based on the analysis of CoNS that reflect the general nosocomial pool and are a reasonable indicator of organisms that cause nosocomial infections in U.S. hospitals.

BETA-LACTAMS

As with *S. aureus*, from 80 to 90% of CoNS produce an inducible beta-lactamase (13), although the substrate profile and genetic basis for enzyme production have not been examined in any detail. However, the most important mechanism for resistance to beta-lactams is production of a low-affinity penicillin-binding protein, PBP2a. This resistance, designated methicillin or oxacillin resistance, effectively precludes therapy with any of the currently available beta-lactam antibiotics (23). The gene encoding PBP2a, *mecA*, is identical by DNA hybridization and nucleotide sequence analysis among all staphylococci with the characteristic phenotype (12, 23, 63). This phenotype is called heterotypic because only a minority of the entire bacterial population (1 in 10^3 to 1 in 10^6 cells) is resistant to more than 10 μg of methicillin or 6 μg of oxacillin per ml. The heterotypic expression of resistance is, in general, more common and the resistant subpopulation smaller among methicillin-resistant CoNS than among methicillin-resistant *S. aureus* strains (11), leading to more difficulty in detecting methicillin resistance among CoNS than among *S. aureus* by standard low-inoculum susceptibility testing (23). This is particularly true for susceptibility testing of such beta-lactam antibiotics as cefamandole and imipenem, which have extremely small resistant subpopulations only detectable by high-inoculum screening or prolonged incubation of isolates in the presence of the drug (16, 44, 80). However, the presence of a smaller resistant subpopulation for some beta-lactams than for others does not seem to correlate with an improved response of infecting CoNS to therapy. In an animal model of *S. epidermidis* endocarditis, cefamandole, imipenem, and nafcillin all failed to cure infections caused by an organism having small subpopulations resistant to these antibiotics in vitro (16, 80). In contrast, vancomycin, gentamicin, and rifampin were effective at reducing the number of organisms in vegetations. These observations have led to the conviction that in vitro testing methods should maximize the identification of CoNS that contain small resistant subpopulations. Phenotypic testing using large inocula or 2% NaCl with longer incubation times improves detection, but genotypic testing that uses PCR or DNA hybridization to identify isolates containing the *mecA* gene offers the best sensitivity (12, 24, 77, 79).

The NNIS has found that ~60% of CoNS isolated and tested in participating hospitals in 1989 were methicillin resistant. Even higher proportions of isolates resistant to methicillin are found if evaluation of susceptibility is confined to the species *S. epidermidis*. In a retrospective study analyzing oxacillin susceptibility data obtained in 1985 and 1986 from 40 large, geographically diverse hospitals (42), Jones et al. found that the percentage of oxacillin-resistant CoNS varied from 35 to 77%, with an average of 51%, similar to the NNIS data (64). In contrast, a prospective study performed by the same group in 1987 and 1988 using a high-inoculum screening test, obtaining only bacteremic isolates, and determining the species of these isolates found a different result. Among 126 *S. epidermidis* isolates, the species representing 79% of the CoNS causing bacteremia, 78% were resistant to oxacillin, with little variation among hospitals (42). Similarly, in another study an analysis of *S. epidermidis* isolates causing prosthetic valve endocarditis within the year following surgery found 84% to be resistant to methicillin (44).

Methicillin resistance also predicts resistance to multiple classes of antibiotics besides beta-lactams. An analysis of 177

* Corresponding author. Mailing address: Medical College of Virginia, 1101 E. Marshall St., Box 980049, Richmond, VA 23298-0049. Phone: (804) 828-9711. Fax: (804) 828-3097. Electronic mail address: GARCHER@GEMS · VCU · EDU.

methicillin-resistant CoNS from different geographic areas performed in 1990 found 61% resistant to gentamicin, 50% resistant to trimethoprim, 75% resistant to erythromycin, 60% resistant to clindamycin, 35% resistant to tetracycline, and 23% resistant to chloramphenicol (13). A high proportion of bacteremic oxacillin-resistant *S. epidermidis* isolates are also multiresistant, with 75% being resistant to erythromycin, 60% being resistant to clindamycin, and 71% being resistant to gentamicin (42). Thus, it is prudent to assume that methicillin-resistant CoNS are multiresistant and to carefully tailor therapeutic regimens to susceptibility test results.

AMINOGLYCOSIDES

Gentamicin and rifampin (see below) are the two antimicrobial agents most active in vitro against susceptible CoNS. Gentamicin is rapidly bactericidal (8, 44), and MICs range from <0.0125 to 0.1 μg/ml (2, 44). Unfortunately, resistance to aminoglycosides has emerged among CoNS and become widespread, reducing their clinical utility (13, 42).

CoNS carry genes encoding the same aminoglycoside-inactivating enzymes that are found in *S. aureus*. The genes encoding the bifunctional enzyme, AAC(6′)-APH(2″), mediating resistance to gentamicin, tobramycin, netilmicin, and amikacin have been found both on plasmids and in the chromosome of CoNS (7, 31, 57, 73). In the United States, plasmid-encoded genes have been found chiefly on a family of large conjugative plasmids. However, while 63% of gentamicin resistance in *S. aureus* was found to be encoded on these plasmids, only 20% of resistance in CoNS was encoded on conjugative plasmids (13). Much of the chromosomally encoded gentamicin resistance in CoNS is probably carried on a transposon similar to the one isolated from *S. epidermidis*, designated Tn*4031* (73). This transposon is in turn similar to Tn*4001*, an element common among Australian gentamicin-resistant *S. aureus* strains (53). The transposons encoding gentamicin resistance in both *S. aureus* and *S. epidermidis* are composite transposons, with the resistance gene bounded by copies of IS*256*, one or both of which provide proven mobility (21, 53, 73).

While virtually all of the clinically important aminoglycoside resistance in CoNS is mediated by the AAC(6′)-APH(2″) enzyme, isolates also carry genes encoding the ANT(4′)-I enzyme mediating resistance to tobramycin and amikacin but not gentamicin (67). This gene is encoded on the small plasmid pUB110, which has been found integrated both into conjugative plasmids and into the chromosome (22, 78). Genes encoding an APH(3′) enzyme mediating resistance to amikacin, kanamycin, and streptomycin have been found in *S. aureus* (29) but have not been sought in CoNS.

The overall prevalence of aminoglycoside resistance among CoNS is difficult to assess, since few surveys include this phenotype and resistance varies among hospitals. However, it is clear that this phenotype has increased markedly since it was first described for *S. aureus* isolates in 1975 and 1976 (69). Culture surveys of CoNS colonizing the skin of cardiac surgery patients at the Medical College of Virginia Hospital found an increase from 20% resistance to gentamicin among CoNS in 1977 to 70% in 1981 (7). Similarly, while only 5% of methicillin-resistant *S. epidermidis* isolates recovered from prosthetic valve endocarditis patients from 1975 to 1977 were gentamicin resistant, 32% were resistant by 1980 (44), and among prosthetic valve endocarditis isolates recovered between 1982 and 1986, 55% were resistant (9). Finally, more than 60% of CoNS recovered after 1986 from a variety of clinical sources have been gentamicin resistant (13). Thus, aminoglycoside resistance is highly prevalent among nosocomial CoNS causing serious infection and is a common phenotype among isolates colonizing the skin of hospitalized patients. This markedly limits the use of combination regimens including gentamicin, which have been shown to be effective in treating deep-seated foreign body infections (43). Although there are few reports of the antimicrobial susceptibility of CoNS causing prosthetic hip joint infections, the increasingly common practice of incorporating aminoglycosides in bone cement should predict that these infecting isolates will also be resistant to these antibiotics (38).

TRIMETHOPRIM

The combination of trimethoprim and sulfamethoxasole (TMP-SMX) has excellent activity against susceptible staphylococci. The MICs of the combination are less than 0.1 μg/ml (20). Furthermore, the antimicrobial combination has been used with success in the therapy of such serious *S. aureus* infections as endocarditis and meningitis (49, 54). Unfortunately, the emergence and dissemination of resistance to trimethoprim among CoNS preclude the use of TMP-SMX for treatment of many infections.

The first reports of widespread trimethoprim resistance among staphylococci in both Australia and the United States came in the early 1980s (6, 52). Resistance was found to be due to the plasmid-encoded production of the trimethoprim target enzyme, dihydrofolate reductase (25, 62). The plasmid-encoded enzyme, DHFR S1, functioned effectively in the bacterial folic acid synthesis pathway but was not inhibited by trimethoprim. Trimethoprim resistance induced high-level resistance to the TMP-SMX combination because of the relatively poor activity of sulfamethoxasole alone. The DHFR S1 gene, designated *dfrA*, was carried in Australian CoNS largely on nonconjugative plasmids (52, 62), while the gene was found among U.S. isolates on both conjugative and nonconjugative plasmids and integrated into the chromosome (33). Furthermore, the identical gene has been found by DNA hybridization in both *S. aureus* and *S. epidermidis*, suggesting horizontal transfer in nature (33). In Australian staphylococci, the plasmid-encoded gene is preceded by an open reading frame that encodes a protein related to the thymidylate synthetases of both prokaryotic and eukaryotic origins (62). The contribution of this gene, *thyE*, to the overall level of trimethoprim resistance is not known. Since the trimethoprim resistance gene(s) is bounded by copies of the insertion sequence IS*257*, and since there are 8-base-pair target sequence duplications characteristic of a replicative transposition event, the element has been designated a transposon (Tn*4003*) (62). However, in its present locations the trimethoprim resistance gene does not appear to have the independent mobility characteristic of a transposon but translocates to other genetic sites by recombination at flanking insertion sequences (73).

There are undoubtedly additional genes mediating trimethoprim resistance in staphylococci; at least seven nonhomologous genes encode different dihydrofolate reductases in gram-negative bacteria. In support of this contention, an *S. aureus dfrA* probe failed to hybridize to any of 10 highly trimethoprim-resistant *S. haemolyticus* isolates (32).

Resistance to >25 μg of trimethoprim per ml was found among 50% of a geographically diverse collection of methicillin-resistant CoNS from the United States; only 14% of methicillin-susceptible isolates were resistant (13). In contrast, 78% of selected *S. epidermidis* isolates from Hungary, Spain, and Switzerland were trimethoprim resistant, but the majority (70%) of these isolates were methicillin susceptible (19).

However, among the few methicillin-resistant isolates analyzed, 65% were resistant to trimethoprim and multiple other antimicrobial agents. International differences in trimethoprim resistance among CoNS undoubtedly reflect variations in the use of antimicrobial agents. However, in the United States, trimethoprim resistance should be considered a major component of the multiresistant phenotype among CoNS.

GLYCOPEPTIDES

While virtually all CoNS, with the exception of *S. haemolyticus* (see below), remain susceptible to vancomycin (MIC, ≤4 or 8 μg/ml), isolates have become less susceptible to teicoplanin (14, 35, 56). This is particularly true of CoNS isolated from patients in Europe, where teicoplanin is approved for general use. In two studies from France, teicoplanin MICs were 8 to 16 μg/ml for 23 and 38% of CoNS. Teicoplanin MICs were 32 μg/ml for 1.7 and 3.2%, indicating resistance (35, 56). Virtually all of the study isolates were methicillin resistant. No isolates showed reduced susceptibility to vancomycin but in one of the studies, teicoplanin resistance was correlated with either vancomycin or teicoplanin use (56). Reduced teicoplanin susceptibility (MIC, ≥8 μg/ml) was most common among *S. haemolyticus* and *S. epidermidis* isolates; *S. epidermidis* comprised 86.5 and 74% of the isolates in the two studies with intermediate susceptibility. Reduced teicoplanin susceptibility has also been seen with *S. epidermidis* and *S. haemolyticus* isolates from the United States, with 7% of *S. epidermidis* isolates and 21% of *S. haemolyticus* isolates moderately susceptible (MIC, 16 μg/ml) and 11% of *S. haemolyticus* isolates resistant (MIC, >16 μg/ml) in one study (14). Both vancomycin and teicoplanin resistance can be easily selected in vitro in *S. haemolyticus* by exposure of isolates to either vancomycin or teicoplanin (56, 65), yet only teicoplanin resistance can be generated for *S. epidermidis* by stepwise exposure of this species to glycopeptides (17). *S. haemolyticus* isolates recovered from patients receiving vancomycin have shown decreases in vancomycin susceptibility when compared to pretherapy isolates (66, 81). While it is difficult to generate vancomycin resistance (MIC, >16 μg/ml) among *S. epidermidis* isolates in vitro, isolates with reduced susceptibility can be selected (17, 37, 56).

Although vancomycin resistance is rarely seen among most clinical isolates of CoNS in the United States and vancomycin continues to be the mainstay of therapy for methicillin-resistant, multiresistant isolates, data from animal studies show that vancomycin is less rapidly bactericidal than either gentamicin or rifampin for methicillin-resistant organisms (80). Since 70 to 80% of CoNS from infections will be methicillin resistant, the decision of whether to use vancomycin or a beta-lactam when treating infections caused by these organisms is less relevant than for it is *S. aureus*.

RIFAMPIN

Rifampin is highly active against more than 90% of CoNS, regardless of the organisms' susceptibility to methicillin (2, 44, 75, 85). MICs range from <0.0125 to 0.1 μg/ml after low-inoculum susceptibility testing but can increase when higher inocula are used (2, 44, 68, 75). This inoculum variation is due to the presence in the colony of highly rifampin-resistant mutants that occur spontaneously at a rate of 1 in 10^6 to 1 in 10^7 cells. Resistance is presumed to be due to a mutation(s) in the gene encoding the beta-subunit of DNA-dependent RNA polymerase, the target of the rifamycin class of antibiotics. However, no specific DNA sequence data that identify the nature or the site of the mutation(s) have been generated for staphylococci.

Resistance selection demonstrated in vitro is also seen in vivo. Rifampin-resistant *S. epidermidis* isolates have been selected from an initially susceptible population in the vegetations of experimentally infected rabbits and in both the blood and valve rings of patients with prosthetic valve endocarditis (10, 80). Likewise, a trial of rifampin prophylaxis to prevent infections in cardiac surgery patients resulted in 75% of patients converting their skin flora to rifampin-resistant CoNS following a single oral dose of the drug (4). The continued susceptibility of CoNS to rifampin among nosocomial isolates in most surveys reflects the low level of hospital use of this antibiotic in the past. However, increased use of the drug in patients with AIDS and widespread use of rifabutin, a related compound, as prophylaxis for *Mycobacterium avium-M. intracellulare* infections (58) may increase the nosocomial reservoir for rifampin-resistant isolates.

FLUOROQUINOLONES

Staphylococci, both methicillin resistant and methicillin susceptible, were found to be uniformly susceptible to the fluoroquinolones ofloxacin and ciprofloxacin when these drugs were introduced in the mid 1980s; MICs for 90% of strains tested ranged from 0.25 to 0.8 μg/ml (83). This led to the use of these agents in situations associated with frequent coagulase-negative staphylococcal infections, such as in febrile neutropenic patients and patients with chronic ambulatory peritoneal dialysis-associated peritonitis. However, in both of these populations widespread ciprofloxacin use led to a change in skin flora to one composed predominantly of ciprofloxacin-resistant CoNS (26, 48, 59). Subsequently, infections with ciprofloxacin-resistant CoNS occurred, presumably as a result of the alteration in indigenous microflora.

Fluoroquinolones act on bacteria by altering the DNA gyrase-DNA association required for DNA supercoiling (60, 83). One mechanism of resistance to quinolones is the spontaneous mutation of the gene encoding the A subunit of DNA gyrase (*gyrA*) so that its action is no longer inhibited (60). Point mutations in *gyrA*, specifically Ser-84→Phe, have been found in *S. epidermidis* isolates resistant to ciprofloxacin and norfloxacin, a change similar to the Ser-84→Leu mutation shown to confer quinolone resistance in *S. aureus* (70). Single point mutations conferring quinolone resistance among CoNS occur spontaneously in vitro at a low rate ($<10^{-9}$) but are found in resistant isolates recovered from patients (60, 70). Single-step mutations seem to confer low-level resistance in *S. aureus*, while high-level resistance requires selection of isolates that contain additional mutations (39). A mutation leading to resistance by a second mechanism has been described for *S. aureus*, *S. epidermidis*, and *S. haemolyticus* (60, 84) and involves a gene called *norA*. Alterations in *norA* or its regulation confer resistance by mediating the enhanced efflux of fluoroquinolones and other, unrelated antibiotics (60). A third resistance locus, designated *cfxB* or *ofxC* for *S. aureus* (76), may also be involved in multistep acquisition of resistance (39), but this locus has yet to be described for CoNS.

As a result of increasing ciprofloxacin usage, the overall incidence of resistance to fluoroquinolones among CoNS also has been steadily increasing over the past several years. In a review of clinical isolates from the United Kingdom in 1987, 99.4% of CoNS were found to be susceptible to ciprofloxacin. Two years later, in 1989, only 92.6% were susceptible (34). At the Medical College of Virginia Hospital only 86% of isolates were susceptible to ciprofloxacin in 1993, while at the McGuire

Veterans Administration Medical Center in Richmond, Virginia, only 71 to 78% of CoNS were susceptible.

Some newer fluoroquinolones are more active than ciprofloxacin against ciprofloxacin-susceptible staphylococcal isolates. For example, clinafloxacin has an MIC range of <0.008 to 0.25 μg/ml, PD 138312 and PD 140248 have ranges of 0.004 to 0.06 μg/ml, and DU6859a has a range of 0.007 to 0.5 μg/ml when ciprofloxacin-susceptible CoNS have been tested with these drugs (40, 47, 60). However, although many of the newer fluoroquinolones have more potent antistaphylococcal activities, fluoroquinolone-resistant mutants have emerged following exposure to the drugs. In addition, ciprofloxacin-resistant CoNS have markedly reduced susceptibility to most of the newer quinolones (40, 47, 74) and an increased frequency of mutation to resistance (74). Increasing levels of resistance to older agents may preclude the use of these newer compounds.

MACROLIDES, LINCOSAMIDES, AND STREPTOGRAMINS

Susceptible CoNS are inhibited by 0.06 to 0.25 μg of erythromycin (36, 55) and ≤0.06 to 0.5 μg of clindamycin (15) per ml, concentrations easily exceeded in human serum. An investigational semisynthetic streptogramin (RP 59500) made of a mixture of group A and group B streptogramins inhibits most CoNS at MICs of 0.03 to 4 μg/ml (MIC_{50}, 0.25 to 0.5 μg/ml), concentrations also exceeded by predicted peak concentrations of the compound in serum (5 to 10 μg/ml) (1, 5, 30). Although macrolides, lincosamides, and streptogramin B have markedly different structures, all have the same target on the 50S ribosomal subunit, where binding interferes with transpeptidation and translocation reactions.

The efficacy of the macrolides, lincosamide, and streptogramin B-type antibiotics (MLS) for CoNS is markedly compromised in practice by widespread resistance to their action. Three-fourths of methicillin-resistant CoNS and one-fourth to one-third of methicillin-susceptible CoNS from clinical specimens are resistant to erythromycin. In general, there is cross-resistance among MLS compounds because of their common target, but differential induction and unique resistance mechanisms lead to numerous exceptions (see below). Since streptogramin A has a different target on the 50S ribosome than streptogramin B, MLS resistance does not predict resistance to RP 59500. However, resistance to streptogramin A has already emerged among staphylococci in Europe, and resistance to the A component results in resistance to the mixture (51).

MLS resistance is mediated by an enzyme that N^6-dimethylates adenine residues at the peptidyl transferase center of 23S rRNA, the MLS target (82). Methylase is encoded by *erm* genes that are on plasmids (*ermC*) or carried on the transposon Tn*554* (*ermA*) or Tn*551* (*ermB*) (72). The major methylase gene in CoNS is *ermC*, but *ermA* is also common among methicillin-resistant CoNS; *ermB* in human CoNS has not been reported (27, 72). Methylase is inducible and induction is specific for macrolides with 14 constituents in their ring structure (erythromycin and clarithromycin) (72, 82). The mechanism of induction is unique and involves unfolding of the secondary structure of the untranslated leader sequence of methylase mRNA in response to ribosomal stalling mediated by the ribosomal binding of erythromycin (translational attenuation) (82). While 15- (azithromycin) and 16-membered macrolides, clindamycin, and streptogramin B are all poor inducers of resistance, once induced, ribosomal methylation mediates equal resistance to all compounds. Furthermore, mutations in the untranslated methylase leader sequence are common, resulting in constitutive resistance to all MLS compounds. In one study, 68% of all MLS resistance among CoNS was constitutive (41). Thus, much of the dissociation between resistances to erythromycin and clindamycin among methicillin-resistant CoNS (50 to 60% resistance to clindamycin, 70 to 80% resistance to erythromycin) is due to differential induction of the *erm* gene. However, mutation of CoNS *erm* genes from inducible to constitutive expression can occur during exposure to clindamycin (46). Therefore, unless a specific alternate mechanism has been identified, any CoNS resistant to erythromycin should be assumed to contain a gene encoding a ribosomal methylase that is capable of mutating to constitutive expression and clindamycin resistance during clindamycin therapy.

The exception to MLS resistance is a mechanism called MS because it mediates resistance to macrolides and streptogramin B but not lincosamides (27, 41). In some instances, MS resistance is mediated by a gene, *msrA*, that encodes an ATP-dependent efflux pump (61). In a survey from the United Kingdom, only 50% of erythromycin-resistant isolates contained *ermC*, while 37% contained *msrA* (27). The majority of CoNS containing the *msrA* gene were species other than *S. epidermidis*. However, in studies from the United States few erythromycin-resistant CoNS lacked one of the *erm* genes, with 87% of isolates containing either *ermC* or *ermA* (41).

Among the newer macrolides, clarithromycin and azithromycin offer no advantage over erythromycin for CoNS. They have equal activities in vitro against susceptible isolates, and there is cross-resistance among resistant isolates (36, 55). In contrast, the investigational semisynthetic streptogramin RP 59500 was found to inhibit all erythromycin-resistant CoNS at concentrations equal to those for erythromycin-susceptible isolates and may therefore be promising for the treatment of multiresistant isolates (1, 5, 30).

TETRACYCLINES

In most series, 70% or more of CoNS are susceptible to tetracycline and related compounds. We found that 65% of a geographically diverse collection of methicillin-resistant CoNS and 75% of methicillin-susceptible isolates were tetracycline susceptible (13). Tetracycline and doxycycline MICs are 0.06 to 0.5 μg/ml for susceptible CoNS, while minocycline MICs are usually slightly lower at 0.015 to 0.25 μg/ml (71).

There are two mechanisms of tetracycline resistance in staphylococci, both of which have been found in CoNS. In one a membrane protein mediates active efflux of the drug, and in the second a cytoplasmic protein reduces the sensitivity of the ribosome to the drug (50). The major gene in staphylococci encoding active efflux [*tet*(K)] is usually plasmid encoded and mediates resistance to tetracycline and doxycycline but not minocycline. The gene encoding the ribosomal protection protein [*tet*(M)] is carried on the chromosome and mediates comparable resistance to minocycline, tetracycline, and doxycycline. Most clinical CoNS seem to bear the *tet*(K) determinant (18). At the Medical College of Virginia Hospital in 1993, 30% of CoNS were tetracycline resistant and minocycline susceptible, while only 3% were resistant to both drugs. Similarly, among 84 tetracycline-resistant CoNS from France, 90% were resistant to tetracycline and susceptible to minocycline; all but one hybridized to a *tet*(K) DNA probe. The remaining 10% resistant to both drugs hybridized to *tet*(M) (18). These results suggest that minocycline could be an alternative antibiotic to use in treating CoNS infections, but there are no published reports to guide one in this use.

A new class of tetracycline analogs called glycylcyclines that is active in vitro against tetracycline-resistant staphylococci

carrying either the *tet*(K) or the *tet*(M) gene has been developed (28, 71). However, for strains carrying the *tet*(K) gene, the minocycline MICs are still lower than those of the glycylcyclines (71). Thus, these new compounds would be of value only for the small number of CoNS that show *tet*(M)-mediated resistance.

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