ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. 1986, p. 545–552
0066-4804/86/100545-08$02.00/0

Vol. 30, No. 4

# In Vitro Susceptibilities of Four Species of Coagulase-Negative Staphylococci

R. J. FASS,[1]* V. L. HELSEL,[1] J. BARNISHAN,[2] AND L. W. AYERS[2]

*Division of Infectious Diseases, Department of Medicine,[1] and Division of Clinical Microbiology, Department of Pathology,[2] The Ohio State University College of Medicine, Columbus, Ohio 43210*

Received 3 April 1986/Accepted 8 July 1986

**The in vitro susceptibilities of 260 strains of coagulase-negative staphylococci to penicillin G, oxacillin, nafcillin, methicillin, cephalothin, and seven non-β-lactam antimicrobial agents were determined and compared with the susceptibilities of 54 strains of *Staphylococcus aureus* with known patterns of susceptibility. Penicillin G susceptibility for *S. aureus*, *Staphylococcus epidermidis*, *Staphylococcus haemolyticus*, and *Staphylococcus hominis* was readily determined by using β-lactamase tests with induced cells and with a standardized microdilution test. MIC criteria for susceptibility used for *S. aureus* were applicable to the coagulase-negative species. Percentages of organisms susceptible were as follows: *S. epidermidis*, 7%; *S. haemolyticus*, 5%; and *S. hominis*, 47%. Oxacillin susceptibility for these four species was readily determined by using a modification of the microdilution test. MIC criteria for susceptibility used for *S. aureus* were applicable to *S. haemolyticus* and *S. hominis*, but alternate criteria were necessary for *S. epidermidis*. Percentages of organisms susceptible were as follows: *S. epidermidis*, 29%; *S. haemolyticus*, 36%; and *S. hominis*, 97%. *Staphylococcus saprophyticus* differed from the other staphylococcal species; all strains were β-lactamase negative and were penicillin susceptible but had higher penicillin G MICs than did susceptible strains of the other species. There was total cross resistance among the penicillinase-resistant penicillins and cephalothin for the coagulase-negative staphylococci as well as for *S. aureus*; oxacillin MICs were more reliable than MICs of the other drugs or a standardized disk diffusion test for distinguishing resistant from susceptible strains. Vancomycin, rifampin, and ciprofloxacin were consistently active against all staphylococci. Erythromycin, clindamycin, gentamicin, and trimethoprim-sulfamethoxazole were more active against oxacillin-susceptible staphylococci than against oxacillin-resistant staphylococci.**

Strains of *Staphylococcus aureus* (coagulase-positive staphylococci) which are resistant to penicillin G are readily recognized by β-lactamase production or by susceptibility tests which similarly define a bimodal population of strains (37, 38). Penicillin G-resistant strains are usually susceptible to penicillinase-resistant penicillins (PRPs) such as methicillin, nafcillin, and oxacillin and to cephalothin, but strains resistant to those drugs have been isolated with increasing frequency. Such strains are called methicillin-resistant *S. aureus* (34, 48). Unlike β-lactamase production, methicillin resistance is not due to plasmid-mediated enzymatic destruction but to the presence of an extra penicillin-binding protein, PBP 2a. The term heteroresistant is often used to refer to methicillin-resistant *S. aureus* because many strains are phenotypically heterogeneous, containing both methicillin-susceptible and -resistant subpopulations of cells. All cells in the heterogeneous cultures probably carry the genetic marker(s) of methicillin resistance but some factor(s) other than PBP 2a probably controls the expression of phenotypic resistance. Frequently, resistance may be recognized only under special growth conditions such as low temperature, high salt concentration, or prolonged incubation, making laboratory identification problematic (9, 17, 18, 34, 46, 48, 50).

A reliable broth microdilution test has recently been described (48) which discriminates methicillin-resistant *S. aureus* strains from susceptible stains with only minor modifications (direct inoculum preparation from colonies grown overnight on agar plates, 2% NaCl supplementation of the broth, and 24 h of incubation) of the standardized dilution test recommended by the National Committee for Clinical Laboratory Standards (38). According to the modified test (48), susceptible strains and resistant strains had the following MIC breakpoints: oxacillin, ≤2 and ≥8 μg/ml; nafcillin, ≤2 and ≥8 μg/ml; methicillin, ≤4 and ≥16 μg/ml; and cephalothin, ≤8 and ≥32 μg/ml. When 24-h MICs were intermediate, incubation was to be continued for 48 h. Testing with only one compound, such as oxacillin, was recommended since cross resistance was complete. The utility of these modifications has been confirmed by others (9).

Historically, coagulase-negative staphylococci have been of lesser medical concern than *S. aureus*. Lately, these organisms have attracted more attention as human pathogens (3, 7, 23, 30, 40, 52, 54). Like *S. aureus*, they may also be resistant to penicillin G, the PRPs, and cephalothin based on similar mechanisms of resistance (2, 3, 16, 23, 43). For susceptibility testing of coagulase-negative staphylococci, MIC and inhibitory zone diameter criteria applicable to *S. aureus* have often been used (9, 34, 37, 38, 48); however, the adequacy of these criteria has been evaluated with small numbers of strains or without species determination (9, 34, 48).

In this study, we used the microdilution susceptibility test of Thornsberry and McDougal (48) to define the susceptibility patterns of 260 strains of the four most commonly isolated species of coagulase-negative staphylococci to penicillin G, methicillin, nafcillin, oxacillin, and cephalothin. Penicillin G MICs were correlated with β-lactamase tests, oxacillin MICs were correlated with results of a standardized

* Corresponding author.

TABLE 1. Results of β-lactamase tests with staphylococci

| Organism[a] | No. tested | No. (%) positive | | | |
|---|---|---|---|---|---|
| | | Acidimetric | | Nitrocefin | |
| | | Uninduced | Induced | Uninduced | Induced |
| *S. aureus* | 54 | 41 (76) | 46 (85) | 42 (78) | 46 (85) |
| *S. epidermidis* | 100 | 37 (37) | 93 (93) | 45 (45) | 93 (93) |
| *S. saprophyticus* | 49 | 0 (0) | 0 (0) | 30 (61)[b] | 30 (61)[b] |
| *S. haemolyticus* | 75 | 58 (77) | 71 (95) | 62 (83) | 71 (95) |
| *S. hominis* | 36 | 10 (28) | 19 (53) | 12 (33) | 19 (53) |

[a] Strains of *S. aureus* were preselected to represent various patterns of susceptibility. Strains of coagulase-negative staphylococci were randomly selected.
[b] Weak reactions.

oxacillin disk diffusion test (37), and cross resistance among PRPs and cephalothin was studied. Fifty-four strains of *S. aureus* with known susceptibility patterns were similarly tested for comparison. Susceptibilities to seven non-β-lactam antimicrobial agents were also determined.

## MATERIALS AND METHODS

**Organisms.** Staphylococci were identified by using a profile of 27 biochemical tests and the interpretive criteria of Kloos and Schleifer (25). Included were 54 strains of *S. aureus*, 100 strains of *S. epidermidis*, 49 strains of *S. saprophyticus*, 75 strains of *S. haemolyticus*, and 36 strains of *S. hominis*. The *S. aureus* strains were selected from stock cultures to represent various patterns of susceptibility to penicillin G and the PRPs; 15 methicillin-resistant *S. aureus* strains were provided by the Centers for Disease Control. Twenty-seven of the forty-nine *S. saprophyticus* strains were urinary isolates provided by the Ohio State University Student Health Service. The other strains were randomly selected isolates from patient specimens submitted to the Microbiology Laboratories of the Ohio State University Hospitals.

**β-Lactamase tests.** All isolates were tested for β-lactamase production by an acidimetric test (Betatest; Medical Wire and Equipment Co., Cleveland, Ohio) and a chromogenic cephalosporin or nitrocefin test (Cefinase; BBL Microbiology Systems, Cockeysville, Md.) with and without penicillinase induction. Colonies growing on agar near 1-μg oxacillin disks were selected as induced strains.

**MICs.** Laboratory standards of antimicrobial agents were supplied by manufacturers, diluted according to instructions, and dispensed into microdilution plates using a MIC-2000 Plus dispensing machine (Dynatech Laboratories, Inc., Alexandria, Va.) in $\log_2$ dilution steps within the range of 0.03 to 64 μg/ml. MICs were determined by a standardized microdilution method (38) in 0.1-ml volumes of cation-supplemented Mueller-Hinton broth (Difco Laboratories, Detroit, Mich.). For oxacillin, nafcillin, methicillin, and cephalothin, 2% NaCl was added to the media (48). Trimethoprim-sulfamethoxazole (TMP-SMZ) was tested in a fixed 1:19 ratio; 0.1 U of thymidine phosphorylase (Burroughs Wellcome Co., Research Triangle Park, N.C.) per ml was added. The inoculum was prepared from growth on a 24-h culture on agar; enough organisms were added to the Mueller-Hinton broth to yield a turbidity equal to a 1 McFarland standard. This was diluted 1:20 in water and disposable inoculators (Dynatech) which deliver 10 μl per well were used to inoculate microdilution trays. Periodic colony counts indicated that the final inoculum was ca. 5 ×

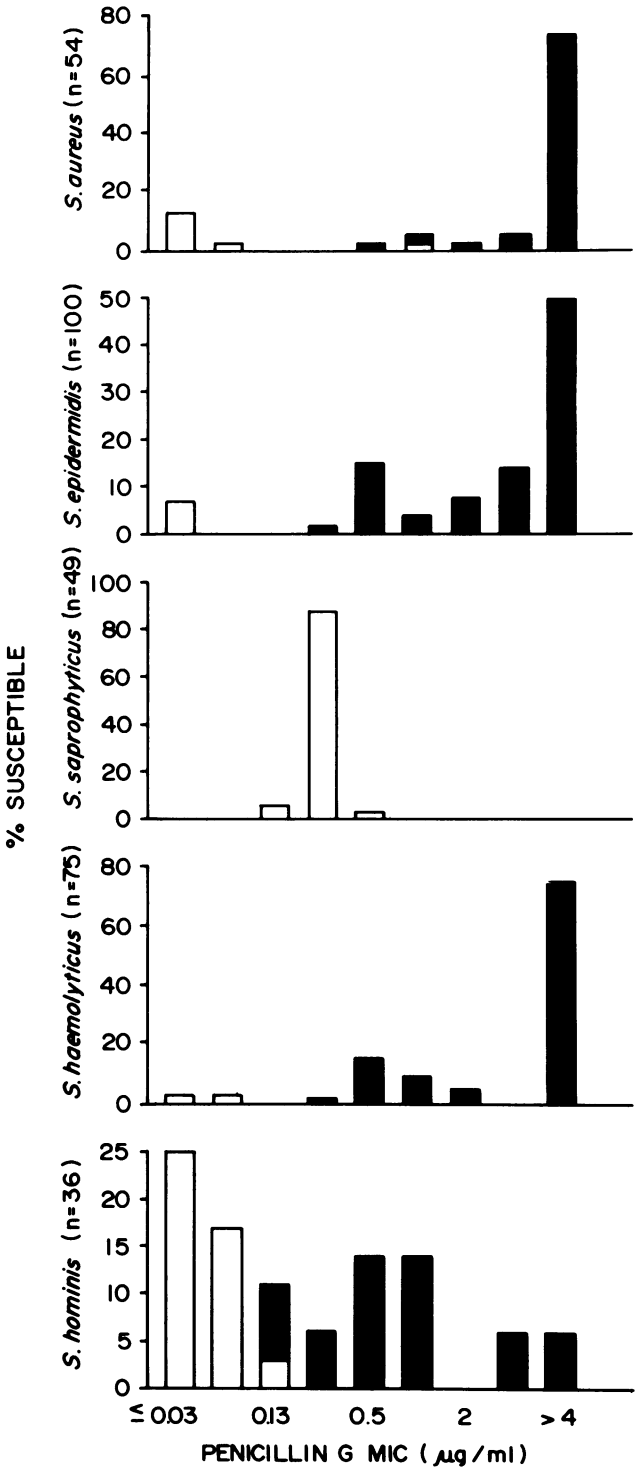


FIG. 1. Frequency distribution of penicillin G MICs for five species of staphylococci. Strains of *S. aureus* were preselected to represent various patterns of susceptibility and strains of coagulase-negative staphylococci were randomly selected. White bars indicate β-lactamase-negative strains, and black bars indicate β-lactamase-positive (acidimetric test) strains.

$10^5$ CFU/ml. The trays were incubated at 35°C. MIC endpoints were determined at 18, 24, and 48 h. The 18-h readings were considered to be the MICs for all drugs except the PRPs and cephalothin. For those drugs, 24-h readings were considered to be the MICs; an increase in MICs of ≥2 dilution steps from 18 to 48 h was considered indicative of heteroresistance.

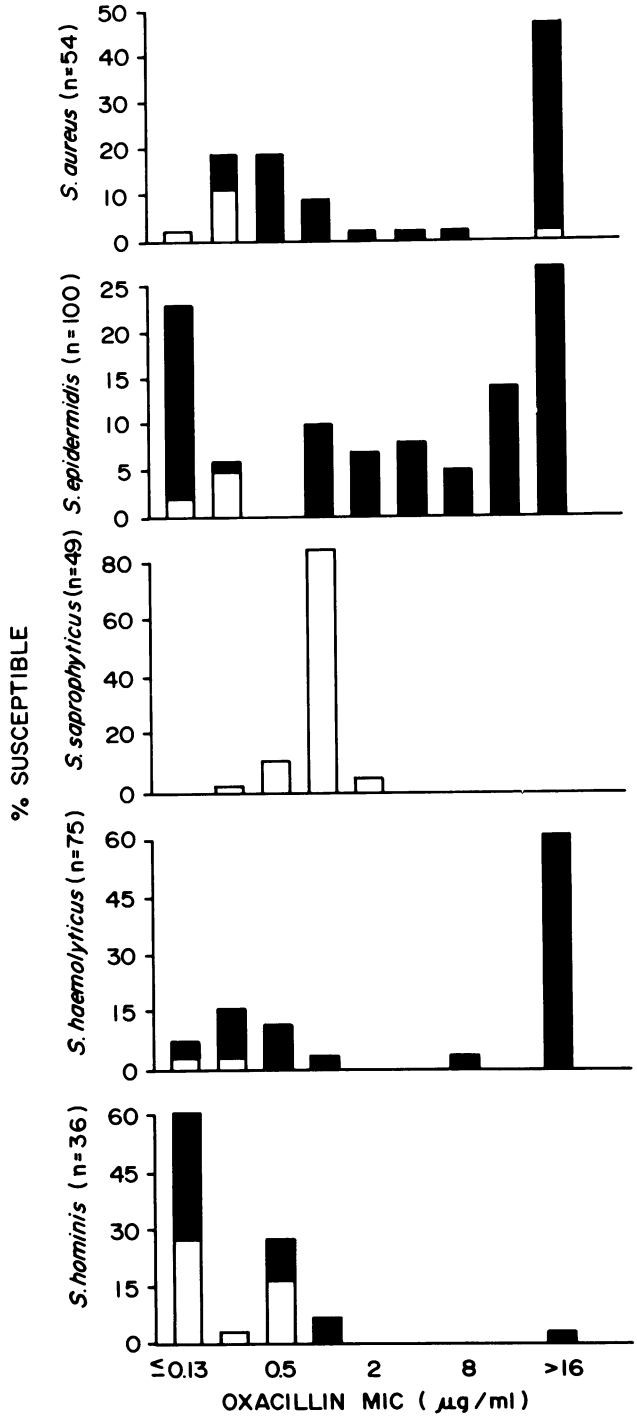


FIG. 2. Frequency distribution of oxacillin MICs for five species of staphylococci. Strains of *S. aureus* were preselected to represent various patterns of susceptibility and strains of coagulase-negative staphylococci were randomly selected. White bars indicate β-lactamase-negative strains, and black bars indicate β-lactamase-positive (acidimetric test) strains.

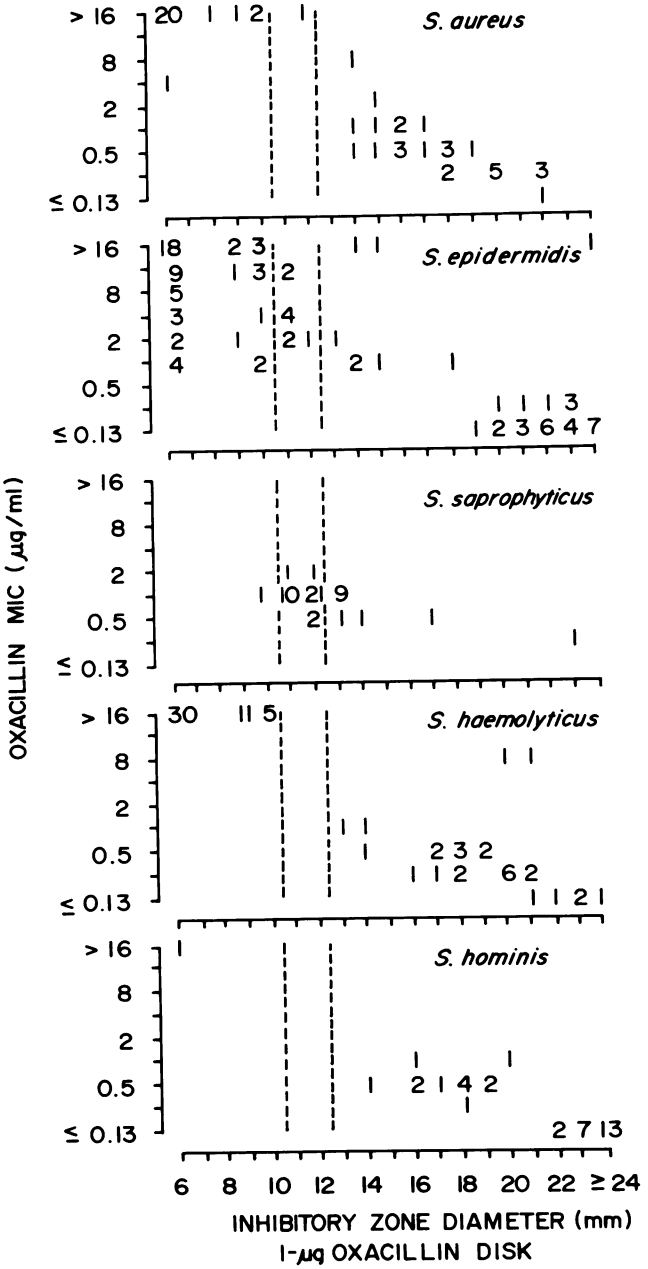


FIG. 3. Correlations of oxacillin MICs and inhibitory zone diameters around 1-μg oxacillin disks for five species of staphylococci. Inhibitory zone diameters were poorly reproducible for resistant strains as defined by MICs (see text); when more than one result was obtained, the first is indicated. Vertical broken lines represent breakpoints recommended by the National Committee for Clinical Laboratory Standards for defining susceptible and resistant strains.

For strains of *S. saprophyticus*, penicillin G MICs in the presence of 4 μg of clavulanic acid per ml were compared with MICs without clavulanic acid to clarify the significance of equivocal β-lactamase tests.

**Disk susceptibility tests.** All isolates were tested for susceptibility to oxacillin by using the 1-μg oxacillin disk according to a standardized method (37).

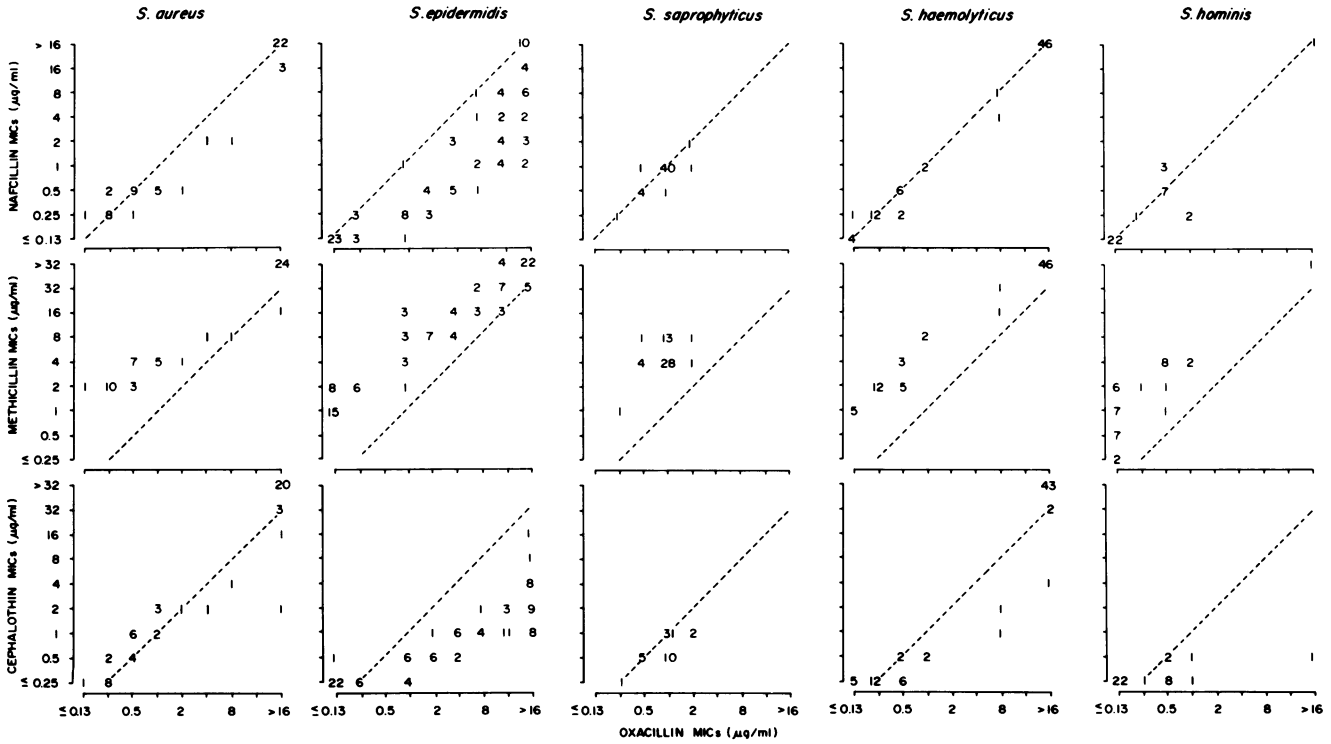


FIG. 4. Correlations of nafcillin, methicillin, and cephalothin MICs with oxacillin MICs for five species of staphylococci. Broken lines represent lines of identity.

## RESULTS

**β-Lactamase.** The results of the β-lactamase tests for the various species of staphylococci are shown in Table 1. Without induction, both the acidimetric test and the nitrocefin test gave false-negative results. With induction, both tests gave identical results, although 30 (61%) of 49 *S. saprophyticus* strains gave negative acidimetric tests and weakly positive nitrocefin tests.

**Susceptibility to penicillin G.** Penicillin G MICs for the various species of staphylococci and the correlation of MICs with β-lactamase production are shown in Fig. 1. For *S. aureus*, *S. epidermidis*, and *S. haemolyticus*, there were bimodal distributions of strains with β-lactamase-negative strains having MICs of ≤0.06 μg/ml and β-lactamase-positive strains having MICs of ≥0.25 μg/ml. The one exception was a β-lactamase-negative, heteroresistant strain of *S. aureus* which had an MIC of 1 μg/ml. There was also a biomodal distribution of penicillin G MICs for *S. hominis* but MICs did not clearly separate β-lactamase-negative from -positive strains. All strains of *S. saprophyticus* had MICs of 0.13 to 0.5 μg/ml; testing in the presence of 4 μg of clavulanic acid per ml did not change results.

**Susceptibility to oxacillin.** Oxacillin MICs for the various species of staphylococci are shown in Fig. 2. For *S. aureus*, *S. haemolyticus*, and *S. hominis*, there were bimodal distributions of strains; the more susceptible strains had MICs ≤ 2 μg/ml, and the more resistant strains had MICs >16 μg/ml; two strains of *S. aureus* and two strains of *S. haemolyticus* had MICs of 4 to 8 μg/ml. MICs of the former did not increase after incubation for 48 h, but MICs of the latter increased to >16 μg/ml. There was also a bimodal distribution of oxacillin MICs for *S. epidermidis*; MICs of ≤0.25 μg/ml identified the more susceptible population, and MICs of ≥1 μg/ml identified the more resistant population. MICs of the 29 strains with 24-h MICs of ≤0.25 μg/ml increased no more than 1 dilution from 18 to 48 h, while MICs for 12 (40%) of the 30 strains with 24-h MICs of 1 to 8 μg/ml increased 2 to ≥5 dilutions from 18 to 48 h. For all four species, β-lactamase-negative strains had the lowest MICs. For *S. saprophyticus* there was a unimodal distribution of MICs; all strains were inhibited by 0.25 to 2 μg/ml.

The correlations of oxacillin MICs and inhibitory zone diameters for the five species of staphylococci are shown in Fig. 3. *S. aureus*, *S. haemolyticus*, and *S. hominis* strains with 24-h MICs of ≤2 μg/ml had inhibitory zone diameters of ≥13 mm, and *S. epidermidis* strains with 24-h MICs of ≤0.25 μg/ml had inhibitory zone diameters of ≥19 mm. All strains with higher MICs had smaller zones of inhibition or zones which were not reproducible; variations up to 15 mm were observed with individual strains tested repeatedly. For *S. saprophyticus*, all strains had MICs of 0.25 to 2 μg/ml, and most had inhibitory zone diameters of 10 to 14 mm.

**Cross resistance among PRPs and cephalothin.** The correlations of nafcillin, methicillin, and cephalothin MICs with oxacillin MICs are shown in Fig. 4. Nafcillin MICs were similar to oxacillin MICs for all species except *S. epidermidis* for which they were up to 5 dilution steps lower. Methicillin MICs paralleled oxacillin MICs for all species and were up to 4 dilution steps higher. Cephalothin MICs were similar to oxacillin MICs for all species except for *S. epidermidis*, for which they were up to 5 dilution steps lower, and for five additional strains—one strain of *S. aureus* (the only penicillinase-negative, oxacillin-resistant strain), three strains of *S. haemolyticus*, and one strain of *S. hominis* (the only PRP-resistant strain).

TABLE 2. Susceptibilities of staphylococci to non-β-lactam antimicrobial agents by oxacillin susceptibility

| Organism | Oxacillin MIC (μg/ml) | No. | % of strains susceptible to antimicrobial agent (μg/ml): | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Vancomycin | | Erythromycin | | Clindamycin | | Gentamicin | | | TMP-SMZ | | | Rifampin (≤0.13) | Ciprofloxacin (≤1) |
| | | | ≤2 | 4–8 | ≤0.5 | ≥8 | ≤0.5 | ≥8 | ≤0.5 | 1–4 | ≥8 | ≤4 | 8–32 | ≥64 | | |
| *S. aureus* | ≤2 | 27 | 100 | 0 | 93 | 7 | 96 | 4 | 96 | 0 | 4 | 100 | 0 | 0 | 100 | 100 |
| | 4–8 | 2 | 100 | 0 | 100 | 0 | 100 | 0 | 100 | 0 | 0 | 100 | 0 | 0 | 100 | 100 |
| | >16 | 25 | 100 | 0 | 12 | 88 | 52 | 48 | 64 | 8 | 28 | 96 | 0 | 4 | 100 | 100 |
| *S. epidermidis* | ≤0.25 | 29 | 100 | 0 | 90 | 10 | 97 | 3 | 100 | 0 | 0 | 94 | 3 | 3 | 100 | 100 |
| | ≥1 | 71 | 100 | 0 | 10 | 90 | 14 | 86 | 27 | 27 | 46 | 65 | 1 | 34 | 100 | 100 |
| *S. saprophyticus* | 0.25–2 | 49 | 100 | 0 | 92 | 8 | 100 | 0 | 100 | 0 | 0 | 98 | 0 | 2 | 100 | 100 |
| *S. haemolyticus* | ≤2 | 27 | 100 | 0 | 85 | 15 | 100 | 0 | 96 | 4 | 0 | 74 | 22 | 4 | 100 | 100 |
| | 8 | 2 | 100 | 0 | 50 | 50 | 100 | 0 | 100 | 0 | 0 | 0 | 50 | 50 | 100 | 100 |
| | >16 | 46 | 89 | 11 | 2 | 98 | 59 | 41 | 15 | 35 | 50 | 4 | 41 | 55 | 100 | 100 |
| *S. hominis* | ≤2 | 35 | 100 | 0 | 80 | 20 | 89 | 11 | 97 | 3 | 0 | 85 | 9 | 6 | 100 | 100 |
| | >16 | 1 | 100 | 0 | 0 | 100 | 0 | 100 | 100 | 0 | 0 | 100 | 0 | 0 | 100 | 100 |

Although the 71 oxacillin-resistant strains of *S. epidermidis* had relatively low nafcillin and cephalothin MICs at 24 h, 45 (63%) of 71 nafcillin MICs and 25 (35%) of 71 cephalothin MICs increased 2 to ≥6 dilutions from 18 to 48 h of incubation. Nafcillin and cephalothin MICs for the 29 oxacillin-susceptible strains did not increase more than 1 dilution with extended incubation.

**Susceptibility to non-β-lactam antimicrobial agents.** The MICs of seven non-β-lactams for the various species of staphylococci are shown in Table 2. All strains were uniformly susceptible to ≤8 μg of vancomycin per ml, ≤0.13 μg of rifampin per ml, and ≤1 μg of ciprofloxacin per ml. Erythromycin and clindamycin MICs were either ≤0.5 μg/ml or ≥8 μg/ml while gentamicin and TMP-SMZ MICs were more variable. Oxacillin-resistant strains of all species were more likely to be resistant to erythromycin, clindamycin, gentamicin, and TMP-SMZ than were oxacillin-susceptible strains.

## DISCUSSION

**Susceptibility to penicillin G.** In this study, *S. epidermidis*, *S. haemolyticus*, and *S. hominis* were similar to *S. aureus* with bimodal distributions of susceptibility to penicillin G. Resistant strains could be distinguished from susceptible strains by tests which detect β-lactamase production from induced cells or by a standardized microdilution test (38). Rare β-lactamase-negative strains of *S. aureus* exist which are resistant to penicillin G based on the methicillin-resistant *S. aureus* phenotype (45), but analogous strains have not been observed among the coagulase-negative species.

*S. saprophyticus* is unique among staphylococci because it causes community-acquired bacteriuria in healthy young females and is susceptible to most antimicrobial agents; other species of coagulase-negative staphylococci are more likely to cause serious nosocomial infections and to be resistant to multiple antimicrobial agents (3, 5, 15, 33, 39). Although studies of β-lactamase production by *S. saprophyticus* have yielded inconsistent and method-dependent results (15, 20, 27, 44), these organisms had a unimodal distribution of penicillin G MICs (5, 15, 33, 39). Based on our studies, we concluded that all strains either were β-lactamase negative or produced ineffective enzyme and were susceptible to penicillin G; application of *S. aureus* MIC criteria was not appropriate to *S. saprophyticus*.

**Susceptibility to oxacillin.** In this study, staphylococci susceptible to penicillin G were susceptible to oxacillin. For penicillin G-resistant strains of *S. aureus*, *S. epidermidis*, *S. haemolyticus*, and *S. hominis*, there was a bimodal distribution of susceptibility to oxacillin which was defined by MICs performed with the modified dilution susceptibility test recommended by Thornsberry and McDougal (48). Their breakpoint for defining susceptibility (≤2 μg/ml) was applicable to *S. aureus*, *S. haemolyticus*, and *S. hominis*, but not to *S. epidermidis*. The heteroresistant phenotype has been more difficult to identify with *S. epidermidis* than with *S. aureus* because strains of *S. epidermidis* have a lower percentage of resistant cells (43). While some studies have indicated low frequencies of resistance for *S. epidermidis* (5, 9, 15, 16, 48, 52), 63 to 87% of strains recovered from patients with prosthetic valve endocarditis or infected cerebrospinal fluid shunts were resistant based on the presence of the heteroresistant phenotype (2, 23). For *S. saprophyticus*, all strains had a unimodal distribution of oxacillin MICs, and this organism should be considered susceptible to oxacillin as well as to penicillin G. The heteroresistant phenotype has not been described for this species as it has for *S. aureus*, *S. epidermidis*, and *S. haemolyticus* (2, 16, 43).

The disk diffusion test was useful in this study when performed in conjunction with MICs to identify heteroresistant strains. However, used alone, two serious problems were observed. First, inhibitory zone diameters with heteroresistant strains of *S. aureus*, *S. epidermidis*, and *S. haemolyticus* were often poorly reproducible with repeated testing, and results occasionally indicated false susceptibility. Second, zone criteria to define susceptibility primarily for *S. aureus* were not applicable to *S. epidermidis* or *S. saprophyticus*. Recommendations to modify the disk test to utilize a 4-μg oxacillin disk have been proposed (34).

**PRP and cephalothin cross resistance.** Cross resistance among the PRPs and cephalothin was complete for all species of staphylococci studied, although many strains of oxacillin- and methicillin-resistant *S. epidermidis* appeared to be nafcillin or cephalothin susceptible. This discrepancy probably occurred because the percentage of nafcillin- and

cephalothin-resistant cells has been determined to be lower than the percentage of methicillin-resistant cells in heteroresistant strains of *S. epidermidis* (2, 36). Subpopulations of cells resistant to nafcillin and cephalothin have been found in every methicillin-resistant isolate but have not always been detectable by susceptibility testing (2). Although some authors have contended that such strains may be cephalothin susceptible based on MIC or inhibitory zone diameter criteria (7, 15, 28, 48, 52), our conclusion that PRP-resistant strains of *S. epidermidis* are also resistant to cephalothin has been supported by other studies which defined resistance based on the heteroresistant phenotype (2, 21, 23, 36) as well as the clinical observation that patients with PRP-resistant *S. epidermidis* bacteremia did not respond well to treatment with cephalosporins (23, 52). There were several possible exceptions to the generalization that PRP-resistant staphylococci are also cephalothin resistant, but these were atypical strains.

Based on its reliability, oxacillin is the preferred drug for disk diffusion testing for all PRPs and cephalothin against staphylococci (22, 34, 37). By using the modified microdilution method (48) and 24 h of incubation, it was also the preferred drug for MIC determinations because it best distinguished resistant from susceptible strains. For the coagulase-negative species, use of an intermediate category of susceptibility and of prolonged incubation to 48 h was unnecessary, although they have occasionally been useful to characterize certain atypical strains of *S. aureus* (35, 48).

The results of oxacillin susceptibility testing should also apply to all the cephalosporins because staphylococci may also be heteroresistant to these drugs (2, 3, 21, 23, 32). If the heteroresistant phenotype defines resistance, susceptibility criteria cannot be based on MIC breakpoints selected by pharmacokinetic considerations or by inhibitory zone diameters determined by regression analysis. Claims that cefamandole is more likely than cephalothin to be active against methicillin-resistant staphylococci have origins in these common methods for defining susceptibility (10, 14, 19). Animal studies (19, 31) have indicated that cefamandole is not therapeutically effective. Furthermore, some cephalosporins such as cefazolin and cefamandole are more susceptible to β-lactamase inactivation than are nafcillin or cephalothin (6, 13, 26, 42); relative susceptibility to staphylococcal β-lactamase has been associated with poor efficacy in both animal (6) and human (42) infections.

**Susceptibility to non-β-lactam antimicrobial agents.** Our study and others (1, 2, 5, 10, 23, 29, 32, 39, 43, 47, 49, 51, 53) have indicated that vancomycin and rifampin are consistently active against both oxacillin-susceptible and -resistant staphylococci. The clinical efficacy of vancomycin has been established for both heteroresistant *S. aureus* (8) and *S. epidermidis* (23, 52). Rifampin has not been used alone because resistance may emerge during treatment (3). Combinations of vancomycin and rifampin have been recommended as giving superior results to those achieved with vancomycin alone (4, 12, 23, 24, 30), although rifampin resistance may also emerge when using this combination to treat both *S. aureus* (11) and *S. epidermidis* (24) infections. Ciprofloxacin and other quinolones have also been consistently active in vitro against methicillin-resistant *S. aureus* (1, 47), and this study indicated similar activity against heteroresistant strains of coagulase-negative staphylococci, but there is too little clinical experience with these drugs to predict their efficacy.

For other antimicrobial agents such as erythromycin, clindamycin, gentamicin, and TMP-SMZ, activity against staphylococci has been inconsistent. The percentages of strains susceptible to specific drugs has varied with the techniques used to perform the susceptibility tests, but heteroresistant strains were more likely to demonstrate multiple resistance than susceptible strains (1, 2, 15, 16, 32, 41, 43, 47, 48). Resistance to aminoglycosides, particularly for *S. epidermidis*, has increased (23, 41), but gentamicin in combination with vancomycin has been recommended for treatment of heteroresistant *S. aureus* (53) and *S. epidermidis* (3, 23, 30) infections. TMP-SMZ was active against oxacillin-susceptible staphylococci and methicillin-resistant *S. aureus* in this study and another (32), but its activity was inconsistent against heteroresistant *S. epidermidis* and *S. haemolyticus* in this study. The use of TMP-SMZ as an oral prophylactic agent in granulocytopenic patients has been associated with an increased frequency of infections caused by *S. epidermidis*, many strains of which were TMP-SMZ resistant (52, 54).

## ACKNOWLEDGMENTS

This work was supported in part by a grant from Hoffmann-LaRoche, Inc., Nutley, N.J.

We thank Clyde Thornsberry, Linda K. McDougal, and Diane Dolan for supplying some of the study strains and Sharon Hein for secretarial assistance.

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