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Evaluation of MicroScan MIC Panels for Detection of Oxacillin-Resistant Staphylococci

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Clinical isolates of staphylococci (420 *Staphylococcus aureus* isolates and 248 coagulase-negative staphylococci) were tested by both MicroScan MIC panels (MicroScan, West Sacramento, Calif.) and an oxacillin agar screen (Mueller-Hinton agar [Difco Laboratories, Detroit, Mich.] containing 6 μg of oxacillin per ml and 4% NaCl) to evaluate the ability of MicroScan to detect oxacillin-resistant strains. MicroScan panels and oxacillin agar screen plates were incubated at 35°C for 24 h and at 30°C for an additional 24 h. Endpoints were recorded at 24 and 48 h. By MicroScan, 23 (5.5%) and 30 (7%) *S. aureus* isolates and 161 (65%) and 162 (65%) coagulase-negative staphylococci were oxacillin resistant at 24 and 48 h, respectively. At both 24 and 48 h, 23 (5.5%) *S. aureus* isolates and 162 (65%) coagulase-negative staphylococci were resistant by the oxacillin agar screen. Five strains for which the oxacillin MIC was 2 or 4 μg/ml and eight strains resistant to oxacillin only at 48 h were further evaluated by broth macrodilution testing for oxacillin with and without clavulanic acid, by oxacillin and amoxicillin-clavulanic acid disk diffusion, and by oxacillin agar screen comparing Mueller-Hinton agars purchased from Difco and BBL Microbiology Systems, Cockeysville, Md. By this additional testing, all 10 *S. aureus* isolates and 1 of 3 coagulase-negative staphylococci examined produced increased amounts of β-lactamase. One coagulase-negative staphylococcus appeared to be truly intermediately oxacillin susceptible. There was no significant difference in the rate of detection of oxacillin resistance between MicroScan and the agar screen. MicroScan panels should be incubated for 24 h only, because prolonged incubation caused strains producing excessive amounts of β-lactamase to appear to be falsely oxacillin resistant.

Methicillin-resistant *Staphylococcus aureus* has been a significant problem in the United States since the mid-1970s (8, 13). In recent years, coagulase-negative staphylococci have been recognized as important nosocomial pathogens (2, 7, 12, 20, 21); therefore, the detection of methicillin resistance in these organisms is also a concern. Because most methicillin-resistant strains are heterogeneous and are recognized only after specific manipulations of culture conditions, various recommendations have been made to enhance their in vitro detection (18, 19, 22). One such method is the oxacillin agar screen (Mueller-Hinton agar [MHA] containing 4% NaCl and 6 μg of oxacillin per ml, 10 μg of methicillin per ml, or 6 μg of nafcillin per ml and incubated at 35°C for 24 h [19]). For MIC testing, the National Committee for Clinical Laboratory Standards standard M7-A (16) recommends testing staphylococci with the following specific modifications: (i) when oxacillin, methicillin, and nafcillin are tested, the broth should be supplemented with 2% NaCl; (ii) the inoculum should be prepared directly from overnight growth on an agar plate; and (iii) incubation should be for a full 24 h at 35°C. Disk diffusion testing should be performed according to National Committee for Clinical Laboratory Standards guidelines (15). Other recommendations have included incubation at 30°C (10) and incubation for 48 h (4, 6).

Many hospital microbiology laboratories, however, use automated rather than the above-described conventional methods of susceptibility testing. It is important, therefore, that these automated systems be able to reliably detect methicillin-resistant staphylococci. MicroScan has changed its MIC panels over the past few years. The earlier panels contained methicillin, which was later replaced with nafcillin. In studies comparing detection of methicillin-resistant staphylococci by these early MicroScan panels and by conventional reference methods, the sensitivity of MicroScan ranged from 80% with methicillin to about 90% with nafcillin (a MIC of >1 μg/ml was considered to indicate resistance) at 24 h (1, 3, 9, 17). There have been few studies examining the present MicroScan panels, which contain oxacillin in broth supplemented with 2% NaCl (5; A. H. Brenner, J. H. Picklo, and S. M. Joern, Abstr. Annu. Meet. Am. Soc. Microbiol. 1987, C109, p. 341). We therefore prospectively tested 668 clinical isolates of staphylococci by MicroScan MIC panels and the oxacillin agar screen to determine the ability of the MicroScan MIC panels to detect oxacillin (methicillin)-resistant *S. aureus* and coagulase-negative staphylococci.

MATERIALS AND METHODS

Organisms. Clinical isolates of staphylococci from all body sites were tested. Of 668 strains, 420 were identified as *S. aureus* by the tube coagulase test (23). The 248 coagulase-negative staphylococci were not further identified. After initial testing, all isolates were stored in sterile defibrinated sheep blood at −70°C. If further testing was required, organisms were subcultured twice on 5% sheep blood agar. The second transfer was used for all testing.

Antimicrobial susceptibility testing. (i) MicroScan MIC panels. Microdilution susceptibility testing was performed according to manufacturer instructions. Briefly, MicroScan MIC panels (MicroScan, West Sacramento, Calif.) were stored at −70°C and allowed to thaw at room temperature

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just before use. From an 18- to 24-h blood agar plate, isolated colonies were emulsified in 0.85% sterile saline to yield a turbidity equal to the density of a 0.5 McFarland standard. The suspension was vortexed, and 0.5 ml was added to 25 ml of sterile distilled water containing 0.02% Tween 80. Panels were inoculated by using the MicroScan inoculator set. The final inoculum ranged from 1×10^5 to 5×10^5 CFU per well, which was confirmed by colony counts periodically throughout the study. Panels were incubated for 24 h at 35°C, and if after incubation for 24 h the oxacillin MIC was ≤4 μg/ml, panels were reincubated at 30°C for an additional 24 h. Endpoints were recorded at 24 and 48 h. Appropriate control organisms were also tested.

(ii) Oxacillin agar screen. MHA (Difco Laboratories, Detroit, Mich.) containing 6 μg of oxacillin (Beecham Laboratories, Bristol, Tenn.) per ml and 4% NaCl was inoculated with approximately 10^4 CFU. The inoculum was prepared by suspending staphylococci from an 18- to 24-h blood agar plate in 0.85% sterile saline to yield a density equal to that of a 0.5 McFarland standard. The agar plates were then spot inoculated with a cotton swab that had been dipped in the suspension (C. Thornsberry, Letter, Antimicrob. Newsl. 1:43–50, 1984). Plates were incubated at 35°C for 24 h, and if the strain was susceptible to oxacillin after incubation for 24 h, it was incubated for an additional 24 h at 30°C. Control strains of oxacillin-resistant and -susceptible *S. aureus* were tested on each plate.

(iii) Broth macrodilution. Susceptibility of the following strains to oxacillin with and without 4 μg of clavulanic acid (Beecham) per ml was tested by broth macrodilution: (i) isolates that were resistant to oxacillin by MicroScan only after incubation for 48 h (seven *S. aureus* isolates and one coagulase-negative staphylococcus) and (ii) other isolates for which the oxacillin MIC was 2 or 4 μg/ml by MicroScan at 24 h (three *S. aureus* isolates and two coagulase-negative staphylococci). One isolate of *S. aureus* for which the oxacillin MIC was 4 μg/ml could not be recovered after storage at −70°C. Broth macrodilution was performed according to National Committee for Clinical Laboratory Standards guidelines (16) with cation-supplemented Mueller-Hinton broth (Remel, Lenexa, Kans.) containing 2% NaCl and incubation at 35°C for 24 h. Serial twofold dilutions of oxacillin ranging from 0.006 to 100 μg/ml were tested. Methicillin-resistant (ATCC 43300) and methicillin-susceptible (oxacillin MIC, 2 to 4 μg/ml) (ATCC 43387) strains of *S. aureus* served as controls.

(iv) Disk diffusion. Disk diffusion testing of the susceptibility of the above-described 13 strains to oxacillin and amoxicillin-clavulanic acid was performed according to National Committee for Clinical Laboratory Standards guidelines (15). The inoculum was prepared directly from 18-h agar plates, and MHA plates (Remel) were incubated at 35°C for 24 h. Controls included *S. aureus* ATCC 43387 and *S. aureus* ATCC 43300.

(v) Oxacillin agar screen MHA comparison. By using the previously described method, the above-indicated 13 staphylococcal strains were retested by oxacillin agar screen to compare MHAs obtained from Difco and BBL Microbiology Systems, Cockeysville, Md. Control strains tested were *S. aureus* ATCC 43300 and *S. aureus* ATCC 43387.

RESULTS

The activity of oxacillin against staphylococci as determined by MicroScan MIC panels and the results of the oxacillin agar screen after incubation for 24 and 48 h are shown in Table 1. With an oxacillin MIC of ≥4 μg/ml representing resistance, 23 (5.5%) strains of *S. aureus* were resistant by MicroScan after incubation for 24 h, and 30 (7%) strains were resistant at 48 h. Of the coagulase-negative staphylococci, 161 (65%) and 162 (65%) strains were oxacillin resistant by MicroScan after incubation for 24 and 48 h, respectively. By agar screen, there were 23 (5.5%) oxacillin-resistant *S. aureus* strains after incubation for both 24 and 48 h and 162 (65%) oxacillin-resistant coagulase-negative staphylococci at both time intervals. For *S. aureus* strains, there were no discrepancies between MicroScan and the agar screen at 24 h; however, for five strains for which the oxacillin MIC was 2 μg/ml after 24 h of incubation the oxacillin MIC was 4 μg/ml after 48 h of incubation, whereas these strains remained susceptible by agar screen. The MIC for one *S. aureus* isolate increased from 1 μg/ml at 24 h to 16 μg/ml at 48 h, but the isolate remained susceptible by agar screen. For the coagulase-negative staphylococci, there was one discrepancy at 24 h between MicroScan and the agar screen; one strain for which oxacillin MICs were 1 and 8 μg/ml at 24 and 48 h, respectively, was resistant by oxacillin agar screen at 24 h.

Thirteen isolates underwent additional testing by broth macrodilution (oxacillin with and without 4 μg of clavulanic acid per ml) and disk diffusion (oxacillin and amoxicillin-clavulanic acid). Moreover, the oxacillin agar screen was repeated with both Difco and BBL MHAs (Table 2). The macrodilution oxacillin MICs for all 10 strains of *S. aureus* were reduced at least fourfold by clavulanic acid, whereas only 2 of the 10 strains were susceptible to amoxicillin-clavulanic acid by disk diffusion. Of the eight *S. aureus* strains for which the MicroScan oxacillin MIC was 2 μg/ml at 24 h, five were intermediate and three were susceptible to oxacillin by disk diffusion. The remaining two strains of *S. aureus*, for each of which the oxacillin MIC was 1 μg/ml at 24 h, increasing to 4 and 16 μg/ml, respectively, at 48 h, were susceptible to oxacillin by disk diffusion.

TABLE 1. Activity of oxacillin against staphylococci by MicroScan and oxacillin agar screen

Organism and incubation time (h)[a]	No. (%) of strains					
	With MicroScan MIC (μg/ml):					Resistant by oxacillin agar screen
	<0.5	1	2	4	>4	
Staphylococcus aureus (*n* = 420)						
24	368 (87)	21 (5)	8 (2)	1 (0.2)	22 (5)	23 (5.5)
48	315 (75)	42 (10)	33 (8)	6 (1.4)	24 (5.7)	23 (5.5)
Coagulase-negative staphylococci (*n* = 248)						
24	85 (34)	1 (0.4)	1 (0.4)	2 (0.8)	159 (64)	162 (65)
48	85 (34)	0	1 (0.4)	1 (0.4)	161 (65)	162 (65)

[a] Incubation was at 35°C for the first 24 h and 30°C for the second 24 h.

TABLE 2. Activity of oxacillin against 13 borderline or intermediately susceptible staphylococci as determined by MicroScan, broth macrodilution, disk diffusion, and agar screen[a]

Organism and isolate no.	MIC (μg/ml)				Disk diffusion[b]		Oxacillin agar screen[c]	
	MicroScan		Macrodilution					
	24 h	48 h	NC	CLAV	OX	A-C	BBL	Difco
Staphylococcus aureus								
142	2	2	3.12	0.78	I	S	S	S
528	2	4	1.56	0.39	I	R	S	S
511	2	4	1.56	0.39	I	R	S	S
597	2	4	1.56	0.39	I	R	S	S
601	2	2	1.56	0.39	S	S	S	S
628	2	4	1.56	0.39	S	R	S	S
649	2	4	1.56	0.1	S	R	S	S
193	2	2	1.56	0.39	I	R	S	S
143	1	4	1.56	0.39	S	R	S	S
409	1	16	1.56	0.39	S	R	S	S
Coagulase-negative staphylococci								
66	4	16	3.12	0.78	I	S	R	R
402	1	8	1.56	1.56	I	S	R	R
588	2	2	1.56	0.78	I	S	S	S

[a] Abbreviations: NC, no clavulanic acid; CLAV, with clavulanic acid; OX, oxacillin, A-C, amoxicillin-clavulanic acid; I, intermediate; S, susceptible; R, resistant.

[b] Zone diameter interpretation: for oxacillin, ≥13 mm = susceptible; ≤10 mm = resistant; 11 to 12 mm = intermediate; for amoxicillin-clavulanic acid, ≥20 mm = susceptible; ≤19 mm = resistant.

[c] Results at 24 and 48 h of incubation were unchanged.

Of the three coagulase-negative staphylococci, the macrodilution oxacillin MIC for only one strain was reduced at least fourfold by clavulanic acid, whereas all three strains were susceptible to amoxicillin-clavulanic acid by disk diffusion. By disk diffusion, all three strains were intermediately susceptible to oxacillin, and corresponding MicroScan MICs at 24 h were 1, 2, and 4 μg/ml. The MIC for the latter strain was reduced fourfold by clavulanic acid.

All *S. aureus* strains were susceptible by the oxacillin agar screen at 24 and 48 h. Of the three coagulase-negative staphylococci, one (for which the oxacillin MIC was 2 μg/ml at 24 and 48 h) was susceptible by the agar screen at 24 and 48 h. The remaining two coagulase-negative staphylococci were resistant by agar screen at 24 h. There were no discrepancies between BBL and Difco MHAs.

DISCUSSION

In our study, we found that for detection of oxacillin-resistant *S. aureus* and oxacillin-resistant coagulase-negative staphylococci the present MicroScan MIC panels (containing oxacillin in broth supplemented with 2% NaCl) used according to manufacturer directions performed comparably to the oxacillin agar screen, which is one of the methods generally accepted as a reference procedure (19). Similar findings have been reported by others (Brenner et al., Abstr. Annu. Meet. Am. Soc. Microbiol. 1987). On the other hand, Coudron et al., who tested a much smaller number of isolates, found that, after incubation for 24 h, MicroScan detected only 75% of methicillin-resistant *S. aureus* (5). The reason for this discrepancy is unclear.

Investigators have demonstrated enhanced detection of heteroresistant staphylococci after incubation for 48 h (4, 6) and by incubation at 30°C (10), although without 2% NaCl supplementation, after 24 h of incubation at 35°C; therefore, if the MicroScan oxacillin MIC was ≤4 μg/ml and/or if the strain was susceptible by oxacillin agar screen, we incubated the isolate at 30°C for an additional 24 h. By doing this, we found that by MicroScan significantly more *S. aureus* strains were oxacillin resistant at 48 h than at 24 h ($P = 0.0078$, McNemar's chi square). This is in contrast to what Brenner et al. observed (Abstr. Annu. Meet. Am. Soc. Microbiol. 1987); however, they incubated panels at 35°C for the entire 48 h, which could account for the disparate results. In contrast to MicroScan results, there was no change in the detection of oxacillin-resistant *S. aureus* or coagulase-negative staphylococci at 24 and 48 h by the oxacillin agar screen.

Prolonged incubation of staphylococci, however, can be problematic, because strains for which the oxacillin MIC is 1 to 2 μg/ml at 24 h may appear resistant to oxacillin at 48 h by virtue of the production of excessive amounts of β-lactamase, as described by McDougal and Thornsberry (14). Moreover, questions addressing the issue of appropriate laboratory and clinical interpretation of staphylococci for which the oxacillin MIC is 2 or 4 μg/ml have recently been raised. Therefore, in an attempt to accurately characterize our isolates that appeared to be borderline susceptible or intermediately susceptible to oxacillin, we examined strains that could be classified as such in greater depth. To detect β-lactamase production, we tested susceptibility to oxacillin with and without clavulanic acid by broth macrodilution, as well as susceptibility to amoxicillin-clavulanic acid by disk diffusion. We performed oxacillin disk diffusion testing. And because BBL MHA has been shown to detect more intrinsic oxacillin-resistant staphylococci than Difco MHA at 24 h (11), we repeated the oxacillin agar screen with both media.

The discrepancies we observed between the two methods used to detect β-lactamase production point out the inability of amoxicillin-clavulanic acid disk diffusion to reliably differentiate excessive β-lactamase-producing strains of staphylococci from truly intermediately susceptible strains. By disk diffusion, only 2 of 10 *S. aureus* strains and all 3 coagulase-negative staphylococci would be considered to be β-lactamase producers, since they appeared susceptible to amoxicillin-clavulanic acid. In contrast, by broth macrodilu-

tion, all 10 *S. aureus* strains and only 1 of the 3 coagulase-negative staphylococci proved to be β-lactamase producers, since the oxacillin MIC for these strains was reduced at least fourfold with the addition of clavulanic acid. Although none of our *S. aureus* strains were truly intermediately susceptible, at least one and possibly two strains of coagulase-negative staphylococci could be classified as such. The one coagulase-negative staphylococcal strain (no. 402) that we believe could be called intermediately susceptible was our only isolate yielding a discrepancy between MicroScan and the oxacillin agar screen at 24 h. This particular strain was susceptible to oxacillin by MicroScan at 24 h (MIC, 1 μg/ml) but resistant at 48 h (MIC, 8 μg/ml). It was intermediately susceptible to oxacillin by disk diffusion and resistant by the agar screen, and its macrodilution oxacillin MIC was unaffected by clavulanic acid. For the possible intermediately susceptible coagulase-negative staphylococcus, the oxacillin MIC was 2 μg/ml at 24 and 48 h by MicroScan and the MIC was 1.56 μg/ml by broth macrodilution, which was reduced only twofold by clavulanic acid. It was intermediately susceptible to oxacillin by disk diffusion and susceptible by the agar screen. Given that intrinsically resistant or heterogeneous staphylococci are often multiply resistant to other antimicrobial agents, we reviewed the MicroScan antibiograms of the 13 strains that underwent additional testing to determine whether the susceptibility patterns would support our above-described classification. Only two strains demonstrated resistance to several antimicrobial agents. The coagulase-negative staphylococcus for which the 24-h oxacillin MIC was 4 μg/ml was resistant to erythromycin, gentamicin, tetracycline, and trimethoprim-sulfamethoxazole. One *S. aureus* strain (no. 193, for which the oxacillin MIC was 2 μg/ml at 24 and 48 h) was resistant to clindamycin, erythromycin, and gentamicin. All other strains were either susceptible to all antibiotics except penicillin or resistant to one agent in addition to penicillin. On the basis of these antibiograms, we could not discern a difference between intermediately susceptible and β-lactamase-producing strains. However, the number of strains we examined was small, and it is possible that with larger numbers a distinction between these types of strains would be apparent.

Because appropriate therapy for borderline-susceptible and intermediately susceptible staphylococci is a significant issue, we attempted to review the charts of the nine patients from whom these 13 strains were recovered. Only six charts could be retrieved, and none of these patients received oxacillin, nafcillin, or methicillin. Only two isolates, one *S. aureus* strain and one coagulase-negative staphylococcus, both of which were recovered from blood, were considered clinically significant, and both patients were treated with vancomycin.

Oxacillin disk diffusion did not provide information helpful in distinguishing intermediately oxacillin-susceptible staphylococci from those capable of excessive β-lactamase production. Moreover, we found no difference between BBL and Difco MHAs, although the number of isolates included in the agar comparison was much too small to allow us to reach a significant conclusion.

In summary, we found that, compared with the oxacillin agar screen, MicroScan reliably detected oxacillin-resistant staphylococci after incubation for 24 h. Moreover, in our opinion, incubation of MicroScan panels should not be extended beyond 24 h. With the exception of one coagulase-negative staphylococcus, prolonged incubation resulted in an interpretation of oxacillin resistance, which in actuality was a consequence of excessive β-lactamase production.

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