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Emergence of High Rates of Antimicrobial Resistance among Viridans Group Streptococci in the United States

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Three hundred fifty-two blood culture isolates of viridans group streptococci obtained from 43 U.S. medical centers during 1993 and 1994 were characterized. Included were 48 isolates of "*Streptococcus milleri*," 219 *S. mitis* isolates, 29 *S. salivarius* isolates, and 56 *S. sanguis* isolates. High-level penicillin resistance (MIC, ≥4.0 μg/ml) was noted among 13.4% of the strains; for 42.9% of the strains, penicillin MICs were 0.25 to 2.0 μg/ml (i.e., intermediate resistance). In general, amoxicillin was slightly more active than penicillin. The rank order of activity for five cephalosporins versus viridans group streptococci was cefpodoxime = ceftriaxone > cefprozil = cefuroxime >> cephalexin. The percentages of isolates resistant (MIC, ≥2 μg/ml) to these agents were 15, 17, 18, 20, and 96, respectively. The rates of resistance to erythromycin, tetracycline, and trimethoprim-sulfamethoxazole were 12 to 38%. Resistance to either chloramphenicol or ofloxacin was uncommon (i.e., <1%). In general, among the four species, *S. mitis* was the most resistant and "*S. milleri*" was the most susceptible.

Viridans group streptococci represent a group of *Streptococcus* species which form part of the commensal bacterial flora of the upper respiratory tracts of healthy humans. The principal species or species groups comprising these streptococci are *S. mutans*, *S. salivarius*, *S. mitis*, "*S. milleri*" (including *S. anginosus*, *S. constellatus*, and *S. intermedius*), and *S. sanguis* (13). These organisms are associated with a relatively narrow spectrum of infections in humans, including subacute bacterial endocarditis usually arising in the face of previously compromised valves (2, 11, 12) and generalized infection in neutropenic patients. Endocarditis most often results from hematogenous seeding from the oral cavity as a result of either poor dentition or extensive dental manipulation. Similarly, the oropharyngeal flora is typically the source of infection in neutropenic patients (1, 4, 5, 7). These associations explain why the American Heart Association recommends chemoprophylactic treatment with agents active against viridans group streptococci for individuals with valvular predisposition who undergo extensive dental manipulations (3). Similarly, empiric therapy of fever in neutropenic patients must take into account this organism group (8).

In the past, viridans group streptococci were nearly uniformly susceptible to β-lactam antimicrobial agents, aminoglycosides, tetracyclines, and macrolides. Several recent published studies, however, indicate that antimicrobial resistance may be emerging as a problem with viridans group streptococci (2, 8, 14). As in *S. pneumoniae*, β-lactam resistance appears to be the result of alterations in penicillin-binding proteins (10). The following questions arise. First, how common is antimicrobial resistance today with this organism group? Second, if resistance is common, what agents might remain of utility against such strains, especially for chemoprophylaxis? These two questions served as the basis for the current investigation.

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MATERIALS AND METHODS

A total of 352 unselected blood culture isolates of viridans group streptococci were obtained in the clinical microbiology laboratories of 43 U.S. medical centers (listed in the Acknowledgments) during 1993 and 1994. All isolates were characterized in the authors' laboratories following shipment of the growth on chocolate agar slants. The organisms were frozen at −70°C prior to characterization.

MICs were determined by the methods described by the National Committee for Clinical Laboratory Standards (NCCLS) (9) with 13 antimicrobial agents by a microdilution method in Mueller-Hinton broth supplemented with 3% lysed horse blood and the following antibiotics at the indicated concentration ranges: penicillin, 0.001 to 32 μg/ml; amoxicillin, 0.008 to 128 μg/ml; cephalexin, 0.015 to 512 μg/ml; cefprozil, 0.002 to 64 μg/ml; cefuroxime, 0.001 to 32 μg/ml; cefpodoxime, 0.001 to 32 μg/ml; ceftriaxone, 0.001 to 32 μg/ml; erythromycin, 0.004 to 128 μg/ml; tetracycline, 0.008 to 256 μg/ml; trimethoprim-sulfamethoxazole (TMP-SMX; 1/19; TMP concentrations = 0.001 to 32 μg/ml); chloramphenicol, 0.25 to 32 μg/ml; RP 59500, 0.004 to 64 μg/ml; and ofloxacin, 0.12 to 16 μg/ml. Laboratory-grade powders obtained from their respective manufacturers were used. Microdilution trays were incubated at 35 to 37°C in ambient air for 22 to 24 h prior to determining the MICs. Daily test controls included *Streptococcus pneumoniae* ATCC 49619, *Haemophilus influenzae* ATCC 49247, and *H. influenzae* ATCC 49766.

Species identification was achieved by use of the API 20S *Streptococcus* identification system (BioMerieux Vitek, Hazelwood, Mo.) and selected conventional biochemical tests by established criteria (13). Selected strains were examined with nucleic acid probes for the genes of *Enterococcus* species and for *S. pneumoniae* (Accuprobe; GenProbe, San Diego, Calif.).

RESULTS AND DISCUSSION

Among the 352 isolates of viridans group streptococci examined in the study, 48 were identified as "*S. milleri*" group, 219 were identified as *S. mitis*, 29 were identified as *S. salivarius*, and 56 were identified as *S. sanguis*. The results of the MIC determinations with seven β-lactam antimicrobial agents versus these 352 organisms are depicted in Table 1. Amoxicillin MICs were generally about one-half those of penicillin for penicillin-susceptible and -intermediate strains. These two agents had equivalent activities against penicillin-resistant organisms. Among the five cephalosporins tested, the rank order of activity was ceftriaxone = cefpodoxime > cefuroxime = cefprozil >> cephalexin. The results of MIC determinations with six non-β-lactam agents against the same organisms are given in Table 2. Broad ranges of MICs were obtained with

TABLE 1. In vitro activities of selected β-lactam antimicrobial agents versus 352 blood culture isolates of viridans group streptococci

Antimicrobial agent	No. (cumulative %) of isolates for which the MIC (μg/ml) is as follows:														% Resistant (breakpoint)[a]
	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	≥64	
Penicillin	8 (2)	2 (3)	20 (9)	55 (24)	69 (44)	83 (67)	23 (74)	24 (81)	21 (87)	19 (92)	22 (98)	3 (99)	2 (99)	1 (100)	13 (≥4)
Amoxicillin	16 (5)	37 (15)	58 (32)	52 (46)	58 (63)	39 (74)	31 (83)	9 (85)	9 (88)	18 (93)	21 (99)	3 (99)	1 (100)		15 (≥2)
Cephalexin				1 (0.3)		2 (1)		11 (4)	32 (13)	77 (35)	95 (62)	48 (76)	25 (83)	63 (100)	96 (≥2)
Cefprozil	2 (0.6)	1 (1)	2 (2)	11 (5)	28 (13)	77 (34)	94 (61)	46 (74)	27 (82)	17 (87)	11 (90)	8 (92)	9 (95)	19 (100)	19 (≥2)
Cefuroxime	1 (0.3)	5 (2)	11 (5)	21 (12)	48 (24)	69 (44)	64 (62)	48 (76)	21 (82)	22 (88)	15 (92)	14 (96)	7 (98)	6 (100)	20 (≥2)
Cefpodoxime	7 (2)	13 (6)	34 (15)	54 (31)	83 (54)	38 (65)	49 (79)	19 (84)	10 (87)	16 (92)	17 (97)	10 (99)	1 (99)	1 (100)	15 (≥2)
Ceftriaxone	2 (0.6)	3 (1)	9 (4)	34 (14)	82 (37)	65 (55)	48 (69)	47 (82)	21 (88)	23 (95)	11 (98)	6 (99)	1 (100)		17 (≥2)

[a] MIC breakpoints for resistance are those recently defined by NCCLS for penicillin and ceftriaxone versus viridans group streptococci. For amoxicillin, the current pneumococcal breakpoint was applied; the ceftriaxone breakpoint was used with cephalexin, cefprozil, cefuroxime, and cefpodoxime.

erythromycin, tetracycline, and TMP-SMX, a narrower range was obtained with pristinamycin, and very tight ranges were obtained with chloramphenicol and ofloxacin. A summary of the in vitro activities of the 13 antimicrobial agents examined in the study versus four species of viridans group streptococci is presented in Table 3. In general, isolates of "*S. milleri*" were most susceptible; *S. mitis* isolates were most resistant.

The results of the present study reveal high rates of β-lactam resistance among current blood culture isolates of viridans group streptococci. By using penicillin MIC breakpoints recently established by the NCCLS for specific application to viridans group streptococci (9a), fewer than one-half of the isolates would have been judged to be susceptible to penicillin. Among 198 resistant isolates (i.e., 56% of the total), roughly three of four (i.e., 43% of the total) were of intermediate resistance (i.e., penicillin MICs, 0.1 to 2.0 μg/ml), with the remaining isolates (i.e., 13% of the total) exhibiting high-level penicillin resistance (i.e., MICs, ≥4.0 μg/ml). On the basis of a resistance breakpoint of ≥2 μg/ml (i.e., the NCCLS amoxicillin resistance breakpoint for *S. pneumoniae*), 15% of all isolates were found to be resistant to amoxicillin. The rates of resistance to cefprozil, cefuroxime, cefpodoxime, and ceftriaxone obtained by using a common breakpoint of ≥2 μg/ml were roughly equivalent (i.e., 15 to 20%). Comparisons of the MICs for individual isolates, however, demonstrated the superior activities of cefpodoxime and ceftriaxone. Cephalexin had limited activity versus viridans group streptococci.

Among the non-β-lactam agents examined in the study, ofloxacin and chloramphenicol were found to have conspicuously lower rates of resistance than erythromycin, tetracycline, and TMP-SMX. With the last three agents, rates of resistance varied between 12 and 38%. Strain-by-strain comparisons revealed near linear relationships between the MICs of these three antimicrobial agents for viridans group streptococci (data not shown). RP 59500, a new streptogramin antimicrobial agent, had activity roughly comparable to that of chloramphenicol on a weight basis. The rates of resistance to this agent cannot be calculated in view of the lack of defined MIC interpretive criteria.

In 1979, Bourgault and colleagues (2) described the low MICs of 12 antimicrobial agents for 63 isolates of viridans groups streptococci from patients with endocarditis at the Mayo Clinic. They observed only two penicillin-resistant strains (i.e., MIC, 4.0 μg/ml), one *S. mitis* strain and one "*S. milleri*" strain. Ten years later, 12 of 63 blood culture isolates (19%) of viridans group streptococci recovered in Italy from febrile neutropenic patients were noted to be of either intermediate or high-level penicillin resistance (14). More recently, in 1993, among 47 blood culture isolates of viridans group streptococci recovered from febrile neutropenic patients in the United Kingdom, 21% revealed intermediate penicillin resistance and 17% had high-level resistance (8).

The results of the current investigation suggest that the rates of antimicrobial resistance of viridans group streptococci versus penicillin and other β-lactam antimicrobial agents continue to increase. In addition, high rates of erythromycin, TMP-SMX, and tetracycline resistance (i.e., 12 to 38%) were observed. As has been shown previously (2, 14), we also noted higher rates of resistance among *S. mitis* isolates than among the other three species of viridans group streptococci examined. Unfortunately, we did not have available for analysis patient information pertaining to individual blood culture isolates such as specific disease associations or patient antibiotic histories. As a result, we are unable to discuss our findings in the context of either of these two issues. Also, the number of isolates from individual medical centers was too small to permit an analysis of rates of resistance by geographic area. Recognizing that significant blood culture isolates of viridans group streptococci are uncommon, individual institutions are encouraged to attempt to define their own rates of resistance.

The recent emergence of antimicrobial resistance compli-

TABLE 2. In vitro activities of selected non-β-lactam antimicrobial agents versus 352 blood culture isolates of viridans group streptococci

Antimicrobial agent	No. (cumulative %) of isolates for which the MIC (μg/ml) is as follows:														% Resistant (breakpoint)[a]
	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	≥64	
Erythromycin	4 (1)	31 (10)	75 (31)	90 (57)	4 (58)	4 (59)	10 (62)	30 (70)	49 (84)	22 (91)	15 (95)	2 (95)		16 (100)	38 (≥1)
Tetracycline	1 (0.3)	4 (1)	3 (2)	8 (5)	96 (32)	89 (57)	14 (61)	17 (66)	13 (70)	14 (74)	14 (78)	28 (86)	39 (97)	12 (100)	12 (≥8)
TMP-SMX		1 (0.3)	5 (2)	12 (5)	53 (20)	80 (43)	84 (67)	35 (77)	24 (84)	24 (90)	18 (95)	14 (99)	2 (10)		16 (≥4)
Chloramphenicol							3 (1)	33 (10)	250 (81)	64 (99)	1 (99)	1 (100)			0.3 (≥16)
Ofloxacin						3 (1)	50 (15)	187 (68)	103 (97)	7 (99)		2 (100)			0.6 (≥8)
RP 59500				1 (0.3)	1 (0.6)	8 (3)	41 (14)	54 (30)	150 (72)	54 (88)	33 (97)	10 (100)			

[a] MIC breakpoints for resistance are those defined by NCCLS for susceptibility tests with viridans group streptococci for all agents except TMP-SMX, for which no breakpoints have been established. For TMP-SMX, the NCCLS resistance breakpoint for TMP-SMX versus *S. pneumoniae* was applied.

TABLE 3. In vitro activities of 13 antimicrobial agents versus individual viridans group streptococcal species[a]

Antimicrobial agent (BP[b])	*S. milleri* (n = 48)			*S. mitis* (n = 219)			*S. salivarius* (n = 29)			*S. sanguis* (n = 56)		
	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	%R	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	%R	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	%R	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	%R
Penicillin (≥4)	0.12	0.25	2	0.25	8	16	0.5	4	17	0.25	2	9
Amoxicillin (≥2)	0.12	0.25	4	0.06	8	19	0.12	4	14	0.25	2	11
Cephalexin (≥2)	4	16	92	8	>512	95	8	32	100	16	64	100
Cefprozil (>2)	0.5	1	4	0.5	32	31	0.5	8	31	0.5	4	23
Cefuroxime (≥2)	0.5	1	6	0.5	16	31	0.25	2	17	0.25	2	14
Cefpodoxime (≥2)	0.5	0.5	2	0.12	8	23	0.12	1	3	0.12	1	5
Ceftriaxone (≥2)	0.5	1	2	0.25	4	24	0.25	4	21	0.25	1	4
Erythromycin (≥1)	0.06	2	13	0.25	4	45	0.06	>128	31	0.06	4	38
Tetracycline (≥8)	0.25	16	17	0.25	32	29	0.25	32	24	0.25	32	27
TMP-SMX (≥4)	0.12	0.25	4	0.5	8	21	0.5	2	7	1	4	14
Chloramphenicol (≥16)	2	4	0	2	4	0.5	2	4	0	2	2	0
RP 59500	2	4		2	8		2	4		2	8	
Ofloxacin (≥8)	1	1	2	1	2	0.5	2	2	0	1	1	0

[a] MIC_{50} and MIC_{90}, MICs at which 50 and 90% of isolates are inhibited, respectively; %R, percent resistant.
[b] BP, MIC breakpoints (in micrograms per milliliter) for resistance as defined by NCCLS for tests with penicillin, ceftriaxone, erythromycin, tetracycline, chloramphenicol, and ofloxacin versus viridans group streptococci. The ceftriaxone breakpoint of ≥2 μg/ml was applied to cephalexin, cefprozil, cefuroxime, and cefpodoxime. The breakpoints for amoxicillin and TMP-SMX were those advocated by NCCLS for tests with *S. pneumoniae.*

cates therapy of viridans group streptococcal infections, e.g., endocarditis and bacteremia in the neutropenic host. However, such infections are usually characterized by the recovery of an isolate from representative clinical specimens. Therefore, definitive therapy can be guided by in vitro susceptibility studies. Chemoprophylaxis for dental procedures and in neutropenic patients is more complicated. The results of the current study suggest that oral penicillins and cephalosporins might have limited value as prophylactic agents. The same appears to be true of the macrolides, tetracyclines, and TMP-SMX. Ofloxacin and chloramphenicol were the most consistently active compounds in the present study. It is tempting to speculate that ofloxacin might be useful as an agent for prophylaxis. Unfortunately, quinolone prophylaxis in neutropenic cancer patients has often been associated with breakthrough bacteremia caused by viridans group streptococci which express high-level quinolone resistance (6, 8). Evidently, under the selective pressure of quinolone prophylaxis, quinolone-resistant strains arise among a previously susceptible population of viridans group streptococci, probably in the upper respiratory tract, and then go on to cause bacteremia. It is possible that newer quinolones with greater activities against gram-positive cocci might function better as chemoprophylactic agents.

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