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Antimicrobial Susceptibilities of *Streptococcus* Species That Cause Septicemia in Neutropenic Patients

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Sixty-three consecutive streptococcal blood isolates from neutropenic patients, represented mainly by viridans group streptococci, were evaluated in vitro for antibiotic susceptibility. Of these isolates, 79.3% were highly susceptible to penicillin (MIC, ≤0.12 μg/ml). Overall, imipenem was the most active agent, followed by teicoplanin and vancomycin. All other agents showed decreased activity against streptococcal isolates that were not highly susceptible to penicillin.

Streptococcal septicemia is a growing problem among patients undergoing intensive cytoreductive chemotherapy (2, 3, 7, 8). At particular risk of infection seem to be patients receiving high doses of cytosine arabinoside or allogeneic bone marrow transplantation for acute lymphocytic leukemia (6, 7). Viridans group streptococci are the most frequent isolates (6, 7); in our center in reçent years, these organisms have represented the leading cause of septicemia, exceeded only by coagulase-negative staphylococci. The response to empiric antibiotics is usually favorable (3, 6–8). However, the clinical presentation may include septic shock, adult respiratory distress syndrome, and encephalopathy without meningitis (6, 7, 10).

In an effort to decrease these infections, prophylactic vancomycin (6) or penicillin (H. F. L. Guiot, P. J. Van Den Broek, J. W. M. Van Der Meer, W. G. Peters, R. Willemze, and R. Van Furth, Program Abstr. 5th Int. Symp. Infect. Immunocompromised Host, abstr. no. 21, 1988) has been suggested for treatment of high-risk patients. However, use of vancomycin may be of concern because of its expense. The emergence of resistance with the widespread usage of vancomycin is another potential concern. On the other hand, use of penicillin may be contraindicated in institutions where penicillin-resistant streptococci are frequently isolated (2).

Given these observations, it seemed appropriate to evaluate the activity of penicillin, vancomycin, and other antibiotics commonly used or potentially useful in the empiric treatment of febrile neutropenic patients or in the prophylaxis of infectious complications against 63 consecutive *Streptococcus* blood isolates. All of these strains were from leukemic patients admitted to the Institute of Hematology of the University of Rome; these strains were considered representative of true bacteremia since they were isolated from at least two blood cultures, performed within 24 h, in the setting of fever and neutropenia. Each strain was identified by the Rapid Strep system, which is reported to identify 85% of commonly occurring species of viridans group streptococci and nearly all group D streptococci (5). Serological procedures were used in conjunction with physiological procedures to identify the beta-hemolytic *Streptococcus* species (4). Viridans group streptococci that could not be identified with the commercial system were identified by the method described by Sands et al. (11).

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The following antibiotics were kindly supplied by their manufacturers: penicillin, ampicillin, and streptomycin (E. R. Squibb & Sons, Princeton, N.J.); piperacillin (Lederle Laboratories, Pearl River, N.Y.); cefamandole and vancomycin (Eli Lilly & Co., Indianapolis, Ind.); cefotaxime (Hoechst-Roussel Pharmaceuticals Inc., Somerville, N.J.); ceftazidime (Glaxo Pharmaceuticals, Ltd., Greenford, United Kingdom); imipenem (Merk Sharp & Dohme, West Point, Pa.); amikacin (Bristol Laboratories, Syracuse, N.Y.); gentamicin (Schering Corp., Bloomfield, N.J.); teicoplanin (Lepetit); and pefloxacin (Rhone-Poulenc). Ceftazidime, vancomycin, and pefloxacin were not evaluated against all available strains. Stock solutions, prepared according to the instruction of the manufacturers, were stored at −70°C until used; the exception was imipenem, stock solutions of which were prepared daily.

MICs were determined by a macrodilution method in cation-supplemented Mueller-Hinton broth with 5% horse blood lysed with saponin (9). An equal volume of organisms from an overnight broth culture was added to serial twofold dilutions of antibiotics to yield a final inoculum of 6×10^5 to 10^6 CFU/ml. The MIC was defined as the lowest concentration of antibiotic that completely inhibited growth after 24 to 48 h of incubation at 35°C in ambient air.

Our streptococcal strains were represented primarily by viridans group streptococci, which accounted for 56 of the 63 (88.8%) consecutive blood isolates (Tables 1 and 2). As previously reported (3, 6, 8), *Streptococcus mitis* was the species most frequently recovered (41%), followed by *S. sanguis* 2 (28.6%), *S. sanguis* 1 (11%), *S. bovis* (4.8%), *S. anginosus* (3.1%), and *S. lactis*, *S. salivarius*, *S. mutans*, *S. morbillorum*, *S. agalactiae*, *S. pyogenes*, and *Enterococcus faecalis* (1.6% each).

Overall, 0.12 μg of penicillin per ml inhibited 79.3% of the organisms evaluated. At the same concentration, ampicillin, piperacillin, cefamandole, cefotaxime, imipenem, and ceftazidime (the latter evaluated against 56 of the 63 strains) resulted in inhibition of 66.6, 69.8, 58.7, 82.5, 90.4, and 32.1%, respectively, of the strains. Twelve strains (six *S. mitis*, two *S. sanguis* 2, one *S. sanguis* 1, one *S. mutans*, one *S. lactis*, and one *E. faecalis*) were moderately susceptible (MICs ≥0.25 and ≤1 μg/ml) or resistant (MICs, >1 μg/ml) to penicillin. Against these organisms, 0.12-μg/ml concentrations of ampicillin, piperacillin, cefamandole, cefotaxime, imipenem, and ceftazidime were inhibitory for 8.3, 25, 16.6,

TABLE 1. Comparative activities of various antibiotics against viridans group *Streptococcus* blood isolates

Organism (no. tested)	Antimicrobial agent	MIC (μg/ml)[a]		
		50%	90%	Range
Streptococcus spp. (56)	Penicillin	0.03	1	≤0.01–4
	Ampicillin	0.03	1	≤0.01–16
	Piperacillin	0.03	2	≤0.01–8
	Cefamandole	0.12	8	0.03–≥32
	Cefotaxime	0.03	1	≤0.01–≥32
	Ceftazidime	0.5	16	0.03–≥32
	Imipenem	≤0.01	0.5	≤0.01–1
	Streptomycin	16	≥128	0.5–≥128
	Gentamicin	2	8	0.06–≥128
	Amikacin	16	≥128	0.12–≥128
	Vancomycin	0.5	1	0.06–2
	Teicoplanin	≤0.01	0.25	≤0.01–1
	Pefloxacin	8	32	0.12–32
S. mitis (26)[b]	Penicillin	0.03	1	≤0.01–4
	Ampicillin	0.03	2	≤0.01–16
	Piperacillin	0.03	2	≤0.01–8
	Cefamandole	0.12	4	0.03–4
	Cefotaxime	0.03	1	≤0.01–8
	Ceftazidime	0.5	16	0.03–≥32
	Imipenem	≤0.01	0.12	≤0.01–0.5
	Streptomycin	8	32	1–≥128
	Gentamicin	1	4	0.06–≥128
	Amikacin	8	64	0.12–≥128
	Vancomycin	0.5	1	0.03–2
	Teicoplanin	0.03	0.25	≤0.01–1
	Pefloxacin	4	32	0.25–32
S. sanguis 1 (7)[c]	Penicillin	0.03		≤0.01–0.25
	Ampicillin	0.03		≤0.01–0.5
	Piperacillin	0.03		≤0.01–0.5
	Cefamandole	0.03		0.03–≥32
	Cefotaxime	0.03		≤0.01–4
	Ceftazidime	0.5		0.03–16
	Imipenem	≤0.01		≤0.01–0.12
	Streptomycin	32		2–≥128
	Gentamicin	2		0.5–8
	Amikacin	32		4–≥128
	Vancomycin	0.5		0.25–1
	Teicoplanin	≤0.01		≤0.01–0.03
	Pefloxacin	16		1–32
S. sanguis 2 (18)[c]	Penicillin	≤0.01	0.25	≤0.01–1
	Ampicillin	≤0.01	1	≤0.01–1
	Piperacillin	≤0.01	0.25	≤0.01–2
	Cefamandole	0.03	4	0.03–≥32
	Cefotaxime	≤0.01	0.06	≤0.01–≥32
	Ceftazidime	0.5	8	0.06–≥32
	Imipenem	≤0.01	0.12	≤0.01–1
	Streptomycin	32	64	0.5–≥128
	Gentamicin	2	32	0.06–64
	Amikacin	32	64	0.5–≥128
	Vancomycin	0.5	1	0.03–0.5
	Teicoplanin	≤0.01	0.25	≤0.01–0.5
	Pefloxacin	16	32	0.12–≥64

[a] 50% and 90%, MIC for 50 and 90% of isolates, respectively.
[b] One strain was not tested for susceptibility to vancomycin, ceftazidime, and pefloxacin; another was not tested for susceptibility to vancomycin and pefloxacin.
[c] One strain was not tested for susceptibility to vancomycin, ceftazidime, and pefloxacin.

41, 66.6, and 0%, respectively, of the strains. As expected, less satisfactory results were obtained with aminoglycosides, which rarely exhibited inhibitory activity at very low concentrations. Pefloxacin also showed poor activity, being inhibitory at easily achievable concentrations in serum (2

TABLE 2. MICs for individual *Streptococcus* isolates

Organisms (no. tested)	Antimicrobial agent	MIC (μg/ml)[a]
Viridans group (5)[b]	Penicillin	$\leq 0.01_3$, 0.03, 2
	Ampicillin	≤0.01, 0.06, 0.25, 0.5, 1
	Piperacillin	≤0.01, 0.03, 0.06_2, 1
	Cefamandole	0.03, 0.12_2, 0.25, ≥32
	Cefotaxime	≤0.01, 0.03, 0.06, 0.12_2
	Ceftazidime	0.06, 0.12, 0.25, 1
	Imipenem	$\leq 0.01_4$, 0.5
	Streptomycin	1, 4, 8, 16, ≥128
	Gentamicin	0.5_2, 1_2, 8
	Amikacin	8_2, 16, 32, ≥128
	Vancomycin	0.06, 0.12_2, 1
	Teicoplanin	$\leq 0.01_2$, 0.03, 0.12, 0.5
	Pefloxacin	0.5, 8, 16, 32
Non-viridans group (7)[c]	Penicillin	$\leq 0.01_2$, 0.03_2, 0.12, 2, 4
	Ampicillin	≤0.01, 0.06_2, 0.12_2, 0.5_2
	Piperacillin	≤0.01, 0.06_2, 0.12, 0.25, 2_2
	Cefamandole	0.06_3, 0.25, 0.5, 16, ≥32
	Cefotaxime	$\leq 0.01_2$, 0.12, 0.25, 1_2, ≥32
	Ceftazidime	0.06, 0.25, 0.5, 1
	Imipenem	$\leq 0.01_5$, 0.5, 2
	Streptomycin	1, 4, 32_2, $\geq 128_3$
	Gentamicin	0.06, 2_2, 4_2, 8, 16
	Amikacin	1, 4, 32, 64, $\geq 128_3$
	Vancomycin	0.06_2, 0.25_2
	Teicoplanin	$\leq 0.01_2$, 0.03_2, 0.12, 0.5_2
	Pefloxacin	2, 4, $\geq 64_2$

[a] Subscript numbers are numbers of isolates for the indicated values.
[b] Other than those listed in Table 1. Includes two *S. anginosus*, one *S. salivarius*, one *S. mutans*, and one *S. morbillorum*; two isolates (*S. anginosus* and *S. salivarius*) were not tested for susceptibility to vancomycin, ceftazidime, and pefloxacin.
[c] Includes three *S. bovis*, one *S. agalactiae*, one *S. lactis*, one *S. pyogenes*, and one *E. faecalis*; three isolates (*S. bovis*, *S. lactis*, and *E. faecalis*) were not tested for susceptibility to vancomycin, ceftazidime, and pefloxacin.

μg/ml) in 29% of 55 evaluated strains. Teicoplanin showed greater activity than did vancomycin. At a concentration of 0.12 μg/ml, teicoplanin inhibited 55 (87%) of the 63 strains, whereas vancomycin inhibited only 10 of 55 (18%) at this concentration. The two drugs showed similar activities against either highly penicillin-susceptible strains (MICs, ≤0.12 μg/ml) or moderately susceptible and resistant strains.

Comparative antibiotic susceptibilities of viridans group *Streptococcus* species, considered both together and separately, and of non-viridans group streptococci are shown in Tables 1 and 2. As previously reported (1), there were no major differences in antibiotic susceptibility between *S. mitis* and *S. sanguis* 2. Because of the small number of *S. sanguis* 2 isolates available in this study, we could not verify whether this species was less susceptible to antibiotics than are other viridans group streptococci (1).

Antimicrobial susceptibility testing of viridans group streptococci is not without technical problems (1). In preliminary experiments for this study, we obtained substantially equal MIC results in 10% CO_2 and in ambient air when cation-supplemented Mueller-Hinton broth with 5% lysed horse blood was used. Overall, only four viridans group streptococci of 56 (7.1%) required 48 h of incubation for determination of MICs. No organism was omitted from the study for poor growth.

In summary, our data indicate that penicillin still provides satisfactory activity against streptococcal isolates causing septicemia in neutropenic patients. Therefore, this drug may be useful in prophylaxis in high-risk patients. Less than 20%

of the streptococcal isolates examined in this study were moderately susceptible or resistant to penicillin. However, they showed decreased susceptibility to all other agents tested except imipenem, teicoplanin, and vancomycin. These antibiotics may prove useful in treatment of septicemias caused by the resistant organisms.

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