ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. 1995, p. 2243–2247 Vol. 39, No. 10
0066-4804/95/$04.00+0

In Vitro Activities of 22 β-Lactam Antibiotics against Penicillin-Resistant and Penicillin-Susceptible Viridans Group Streptococci Isolated from Blood

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Received 17 March 1995/Returned for modification 6 June 1995/Accepted 9 August 1995

A total of 410 strains of viridans group streptococci isolated consecutively from blood were tested by the microdilution method for in vitro susceptibility to 22 β-lactam antibiotics. One hundred thirty-eight strains (33.6%) were resistant to penicillin with a MIC range of 0.25 to 8 μg/ml. MICs of all β-lactam agents tested were higher for penicillin-resistant strains than for susceptible strains. These antibiotics were classified into three groups according to their in vitro activities (MICs at which 50 and 90% of the isolates are inhibited). β-Lactams of the first group (these included imipenem, cefpirome, FK-037, cefditoren, cefotaxime, ceftriaxone, and cefepime) showed activities higher than or similar to that of penicillin against penicillin-resistant viridans group streptococci. However, 80% of highly penicillin-resistant *Streptococcus mitis* organisms required cefotaxime and ceftriaxone MICs of ≥2 μg/ml (range, 2 to 16 μg/ml). β-Lactams of the second group (cefpodoxime, ampicillin, amoxicillin-clavulanate, piperacillin, and cefuroxime) showed lower activities than penicillin. Finally, antibiotics of the third group (cephalothin, oxacillin, ceftazidime, cefixime, cefaclor, cefetamet, cefadroxil, cephalexin, and ceftibuten) showed poor in vitro activities. Therefore, some of the β-lactam agents included in the first group could be an acceptable alternative in the treatment of serious infections due to strains highly resistant to penicillin, although clinical experience is needed.

Viridans group streptococci continue to be the most common cause of both native valve endocarditis (3, 23, 37, 38) and late prosthetic valve endocarditis (9). They have also been implicated in serious pyogenic infections (19, 30, 33, 34, 39). These organisms have been noted as emerging pathogens in neonates (4), and they appear to be a serious problem in patients with hematologic malignancies receiving cytotoxic chemotherapy (2, 5, 6).

Although this group of organisms was generally considered to be uniformly susceptible to penicillin, strains showing penicillin resistance were reported in 1962 in the gingival flora of patients receiving penicillin prophylaxis for rheumatic fever (26). In 1978, penicillin-resistant viridans group streptococci were also found in the oropharyngeal flora of South African children, in association with the emergence of high-level penicillin-resistant *Streptococcus pneumoniae* (14). Since 1983, there have been several reports disclosing high rates of penicillin-resistant viridans group streptococci isolated from clinically significant infections (18, 19, 31, 33), especially those of neutropenic patients (6, 36). In Spain, the prevalence of penicillin-resistant pneumococci (15, 21) and viridans group streptococci (1, 12, 22, 24, 35) in the last decade is among the highest reported in the world. Penicillin resistance in viridans group streptococci and *S. pneumoniae* is due to alterations in penicillin-binding proteins with lowered affinity for this antibiotic (14, 20, 33). These altered forms of penicillin-binding proteins appear to be related to mutation-intraspecific and -interspecific gene transfer from related species (8, 11, 32).

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To date, there is a lack of information regarding the antimicrobial susceptibilities to different β-lactam antibiotics of penicillin-resistant viridans group streptococci. This study was performed to determine the susceptibilities of 410 consecutive viridans group streptococcal isolates from blood to 12 β-lactam antibiotics. One hundred twenty of these strains (70 penicillin-susceptible, 25 intermediately resistant, and 25 highly resistant strains) were studied for 10 other β-lactams, in order to find alternative therapies for infections caused by penicillin-resistant strains.

(This work was partially presented at the 6th European Congress of Clinical Microbiology and Infectious Diseases, Seville, Spain, 1993 [abstract 1017].)

MATERIALS AND METHODS

Organisms. A total of 410 consecutive strains of viridans group streptococci isolated from blood between January 1988 and December 1993 in the Hospital de Bellvitge (Barcelona, Spain) were tested for antimicrobial susceptibility. Only one isolate per patient was tested. These strains were recovered from adult patients whose mean age was 49 ± 21 (standard deviation) years. Two hundred twenty-seven (68%) of them were male, and 131 (32%) were female; 99 (24%) patients had hematologic malignancies, and 34 of the patients (8.3%) had endocarditis. Blood cultures were done, from 1988 to 1989, by using the Roche Septicheck system (Hoffman-La Roche, Inc., Nutley, N.J.). From 1990 on, the samples were inoculated into BACTEC bottles and tested on a BACTEC NR 860 instrument (Johnston Laboratories, Inc., Towson, Md.). The strains were stored at −40°C in skim milk and subcultured on blood agar plates.

The identification of viridans group streptococci has caused much confusion. Currently, in clinical microbiology, conventional biochemical tests remain the methods of choice for identification of these organisms. Therefore, alpha-hemolytic and nonhemolytic streptococci were identified to species level according to standard methods (13). Colony morphology was evaluated, and pure cultures were tested for production of acid from trehalose, sorbitol, lactose, mannitol, sucrose, inulin, raffinose, glycerol, arabinose, maltose, and sorbose. The isolates were additionally tested for reaction in esculin and bile esculin agar, growth in 6.5% sodium chloride broth, ammonia production from arginine, pyruvate utilization, sodium hippurate hydrolysis, and hydrolysis of starch. We used the

taxonomy and nomenclature proposed by Coykendall (10), which include five species, or groups: *Streptococcus mitis*, *Streptococcus sanguis*, *Streptococcus anginosus*, *Streptococcus salivarius*, and *Streptococcus mutans*. Although there was not a general agreement among the investigators about the best classification of this heterogeneous group of organisms, the phenotypic scheme proposed by Coykendall (10) provides enough microbiological information to be used for clinical purposes.

Antimicrobial agents. The following antimicrobial agents were studied for all 410 strains: penicillin (C.E.P.A., S.A., Madrid, Spain), ampicillin (SmithKline Beecham, London, United Kingdom), oxacillin (SmithKline Beecham), amoxicillin-clavulanate (SmithKline Beecham), cephalothin (Eli Lilly & Co., Indianapolis, Ind.), cefuroxime (Glaxo Research Laboratories, Greenford, United Kingdom), cefotaxime (Roussel Ibérica S.A., Madrid, Spain), ceftriaxone (Roche Laboratories, Nutley, N.J.), cefepime (Bristol-Myers Squibb, Syracuse, N.Y.), cefpirome (Roussel Ibérica S.A.), cefpodoxime (Roussel Ibérica S.A.), and imipenem (Merck Sharp & Dohme, West Point, Pa.). In addition, the in vitro activities of 10 other β-lactam antibiotics against 120 of these strains were studied (70 penicillin-susceptible, 25 intermediately resistant, and 25 highly resistant strains). The antibiotics were piperacillin (Lederle Laboratories, Pearl River, N.Y.) cefaclor (Eli Lilly & Co.), cefadroxil (Bristol-Myers Squibb), cephalexin (Eli Lilly & Co.), ceftazidime (Glaxo Research Laboratories), cefixime (Merk-Igoda S.A., Laboratorios Dr. Esteve S.A., Barcelona, Spain); cefetamet (Roche Laboratories) ceftibuten (Schering Corporation, Bloomfield, N.J.), cefditoren (Tedec-Meiji, Farma S.A., Madrid, Spain), and FK-037 (R. W. Johnson Pharmaceutical Research Institute, Southampton, United Kingdom).

Susceptibility testing. MICs were determined by the microdilution method, using cation-adjusted Mueller-Hinton broth supplemented with lysed horse blood (final concentration, 2.5%) as recommended by the National Committee for Clinical Laboratory Standards (28). The inoculum was prepared by suspending several colonies from an overnight blood agar culture in sterile 0.9% saline and adjusting the turbidity to 0.5 McFarland standard. The suspension was further diluted within 15 min to provide a final concentration of bacteria of 5×10^5 CFU/ml in each well of the microdilution trays. The plates were covered with plastic tape and incubated in ambient atmosphere at 35°C for 20 to 24 h. MIC was defined as the lowest concentration of penicillin which inhibited visible growth. Strains were classified for penicillin susceptibility according to the National Committee for Clinical Laboratory Standards criteria (27), as follows: susceptible, MIC ≤ 0.12 μg/ml; intermediately resistant, MIC = 0.25 to 2 μg/ml; and highly resistant, MIC ≥ 4 μg/ml. *S. pneumoniae* ATCC 49619 and *Staphylococcus aureus* ATCC 29213 were used for the quality control.

RESULTS

Among 410 strains of viridans group streptococci isolated, the following species were identified: 205 *S. mitis* strains, 100 *S. anginosus* strains, 72 *S. sanguis* strains, 32 *S. salivarius* strains, and 1 strain of *S. mutans.*

One hundred thirty-eight of the isolates (33.6%) showed decreased susceptibility to penicillin (MICs, 0.25 to 8 μg/ml); 101 (24.6%) were intermediately resistant; and 37 (9%) were highly resistant. There were statistically significant differences in the percentages of penicillin resistance among streptococcal species, which were as follows: 41.5% of *S. mitis*, 41.7% of *S. sanguis*, 28.1% of *S. salivarius*, and 14% of *S. anginosus* ($P < 0.01$).

S. mitis was the species most frequently isolated (50% of all strains). The percentage of strains highly resistant to penicillin was significantly higher in *S. mitis* (16.1%) ($P < 0.0001$) than in *S. salivarius* (6.3%) and *S. sanguis* (2.8%). No high-level penicillin resistance was detected in *S. anginosus* (Fig. 1).

MICs of all β-lactam antibiotics tested were higher for penicillin-resistant strains than for susceptible strains. β-Lactam agents were classified into three groups according to antimicrobial activity (see Tables 1, 2, and 3). The antibiotics in the first group (Table 1) had activities that were better than or similar to that of penicillin against penicillin-resistant viridans group streptococci; these included imipenem, cefpirome, FK-037, cefditoren, cefotaxime, ceftriaxone, and cefepime. The first four of these β-lactams—imipenen, cefpirome, FK-037, and cefditoren—were more active than penicillin against all penicillin-resistant strains, whereas cefotaxime, ceftriaxone, and cefepime showed activities similar to that of penicillin against those strains.

The second group (Table 2) of β-lactams, with slightly lower activities than penicillin, included cefpodoxime, ampicillin, amoxicillin-clavulanate, piperacillin, and cefuroxime.

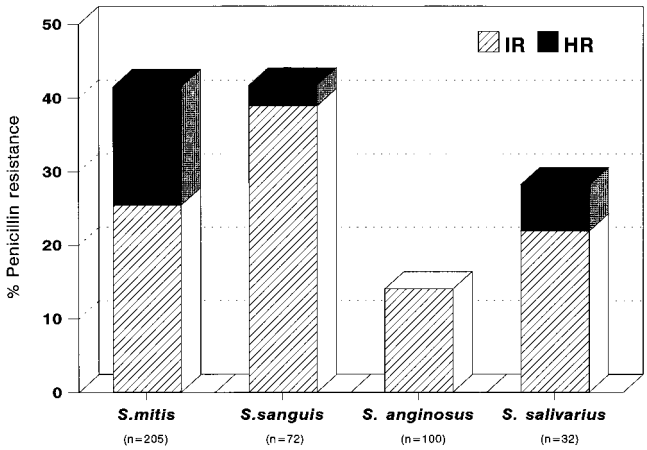

FIG. 1. Comparison of penicillin resistance among streptococcal species. IR, intermediately resistant to penicillin (MIC, 0.25 to 2 μg/ml). HR, highly resistant to penicillin (MIC, ≥4 μg/ml).

Table 3 shows the third group of β-lactams, which have poor in vitro activities. This group includes cephalothin, oxacillin, ceftazidime, cefixime, cefaclor, cefetamet, cefadroxil, cephalexin, and ceftibuten.

DISCUSSION

Resistance to penicillin among clinical isolates of viridans group streptococci is increasingly recognized (1, 12, 18, 19, 22, 24, 32, 33, 35). In this study we observed a high prevalence of penicillin resistance (33.6%) among viridans group streptococci recovered from blood. *S. mitis* was the species most frequently isolated (50% of all isolates) and showed the highest proportion of high-level penicillin resistance. These results are in agreement with those previously reported from South Africa (32) and Spain (1, 24, 35). Penicillin resistance among viridans group streptococci is particularly high in countries like South Africa and Spain, where the incidence of penicillin-resistant pneumococci is also among the highest reported to date. The intrinsic penicillin resistance mechanism in *S. pneumoniae* and viridans group streptococci involves alterations of the target enzymes for β-lactams, essential penicillin-binding proteins, with a decreased affinity of all β-lactam antibiotics (14, 20, 33). Several in vitro studies have demonstrated the potential for transfer of penicillin resistance determinants between these related species (8, 11, 32). These mechanisms together with selective antibiotic pressure may play a role in the emergence and spread of penicillin resistance in viridans group streptococci.

Our study found that viridans group streptococci resistant to penicillin also showed a decreased susceptibility to all β-lactam agents tested. Our classification of β-lactam antibiotics into three groups according to their different degrees of in vitro activity may have important clinical implications. Problems of special clinical concern are the antibiotic management of neutropenic cancer patients and the treatment of endocarditis (7). Among the β-lactams currently used for neutropenic cancer patients with fever, imipenem remains the agent most active against penicillin-resistant strains (6, 25). In our study, imipenem was the most active drug tested and had MICs that were one to five times lower than those of penicillin. However, it should be noted that 54% of highly penicillin-resistant *S. mitis*

TABLE 1. In vitro activities of β-lactam antibiotics which showed activities similar to or higher than that of penicillin against penicillin-resistant viridans group streptococci isolated from blood

Antibiotic[a]	MIC (μg/ml)[b]		
	Range	50%	90%
Penicillin			
S	≤0.03–0.12	0.06	0.12
IR	0.25–2	1	2
HR	4–8	4	8
Imipenem			
S	≤0.03–0.12	≤0.03	0.06
IR	≤0.03–2	0.12	0.5
HR	0.12–4	1	2
Cefpirome			
S	≤0.03–0.5	0.06	0.12
IR	≤0.03–2	0.25	1
HR	0.12–8	1	4
FK-037[c]			
S	≤0.03–0.12	≤0.03	0.06
IR	≤0.03–2	0.25	1
HR	0.5–8	2	4
Cefditoren[c]			
S	≤0.03–0.12	≤0.03	0.12
IR	0.12–8	0.25	1
HR	1–8	2	4
Cefotaxime			
S	≤0.03–1	0.06	0.25
IR	0.12–8	0.5	2
HR	0.5–16	4	8
Ceftriaxone			
S	≤0.03–1	0.12	0.25
IR	0.12–4	0.5	2
HR	1–8	4	8
Cefepime			
S	≤0.03–1	0.06	0.25
IR	0.12–4	0.5	2
HR	1–16	4	8

[a] S (n = 272), susceptible to penicillin (MIC, ≤0.12 μg/ml); IR (n = 101), intermediately resistant to penicillin (MIC, 0.25 to 2 μg/ml); HR (n = 37), highly resistant to penicillin (MIC, ≥4 μg/ml).
[b] 50% and 90%, MICs at which 50 and 90% of the isolates are inhibited, respectively.
[c] Only 120 strains were studied (70 S, 25 IR, 25 HR).

strains showed imipenem MICs of 1 μg/ml and 36.4% had MICs of 2 μg/ml. Newer extended-spectrum cephalosporins (cefpirome, FK-037, and cefditoren) had good in vitro activity against penicillin-resistant strains, although no clinical experience has been reported.

Over the last 5 years, several studies have evaluated different therapeutic regimens for endocarditis caused by viridans group streptococci. Ceftriaxone is considered a reasonable alternative for the outpatient treatment of viridans group streptococcal endocarditis. This agent has excellent in vitro activity and favorable pharmacokinetic properties. The combination of ceftriaxone and netilmicin was more effective than either agent alone in a rat model of infective endocarditis caused by β-lactam-susceptible and -resistant strains of viridans group streptococci (17). In another study, a single daily dose of ceftriaxone for 4 weeks resulted in an effective and safe treatment of endocarditis due to penicillin-susceptible streptococci (16). However, our data show that ceftriaxone and cefotaxime MICs of highly penicillin-resistant *S. mitis* strains were ≥2 μg/ml in more than 80% of these isolates (MICs, 2 to 16 μg/ml). In addition, highly penicillin-resistant strains required cefotaxime MICs that were lower than, similar to, or higher (1 to 3 dilutions) than those of penicillin in 43.9, 31.7, and 24.4% of the strains, respectively. Currently, reliable interpretative criteria for resistance to extended-spectrum cephalosporins and carbapenems in these microorganisms are not available. Only for related species such as *S. pneumoniae* have MIC standards for interpretative criteria for resistance to cefotaxime, ceftriaxone, and cefepime (MICs ≥ 2 μg/ml) recently been reported by the National Committee for Clinical Laboratory Standards (29).

The antimicrobial agents with slightly lower in vitro activities than penicillin against viridans group streptococci (cefpodoxime, ampicillin, amoxicillin-clavulanate, piperacillin, and cefuroxime) and the β-lactams which showed poor in vitro activities (cephalothin, oxacillin, ceftazidime, cefixime, cefaclor, cefetamet, cefadroxil, cephalexin, and ceftibuten) have, consequently, limited application in clinical infections.

In conclusion, our study shows a high prevalence of penicillin-resistant viridans group streptococci isolated from blood. These resistant strains showed various degrees of diminished susceptibility to all β-lactam agents. The most active drug was

TABLE 2. In vitro activities of β-lactam antibiotics which showed activities lower than that of penicillin against penicillin-resistant viridans group streptococci isolated from blood

Antibiotic[a]	MIC (μg/ml)[b]		
	Range	50%	90%
Penicillin			
S	≤0.03–0.12	0.06	0.12
IR	0.25–2	1	2
HR	4–8	4	8
Cefpodoxime			
S	≤0.03–2	0.12	0.5
IR	0.12–8	0.5	2
HR	2–16	8	16
Ampicillin			
S	≤0.06–1	0.12	0.25
IR	0.25–8	2	4
HR	4–16	16	16
Amox-clav[c]			
S	≤0.06–1	0.25	0.25
IR	0.25–4	1	4
HR	4–>16	8	16
Piperacillin[d]			
S	≤0.03–2	0.25	0.5
IR	1–8	2	8
HR	4–16	8	16
Cefuroxime			
S	≤0.03–2	0.25	0.5
IR	0.25–32	1	4
HR	2–>32	8	32

[a] S (n = 272), susceptible to penicillin (MIC, ≤0.12 μg/ml); IR (n = 101), intermediately resistant to penicillin (MIC, 0.25 to 2 μg/ml); HR (n = 37), highly resistant to penicillin (MIC, ≥4 μg/ml).
[b] 50% and 90%, MICs at which 50 and 90% of the isolates are inhibited, respectively.
[c] Amox-clav, amoxicillin-clavulanate.
[d] Only 120 strains were studied (70 S, 25 IR, 25 HR).

TABLE 3. β-Lactam antibiotics which showed poor in vitro activities against penicillin-resistant viridans group streptococci isolated from blood

Antibiotic[a]	MIC (μg/ml)[b]		
	Range	50%	90%
Penicillin			
S	≤0.03–0.12	0.06	0.12
IR	0.25–2	1	2
HR	4–8	4	8
Cephalothin			
S	≤0.03–4	0.5	1
IR	0.25–32	4	16
HR	2–>32	32	>32
Oxacillin			
S	≤0.25–8	0.5	1
IR	0.5–16	4	16
HR	4–>32	16	>32
Ceftazidime[c]			
S	0.06–16	1	4
IR	1–>32	4	16
HR	16–>32	32	>32
Cefixime[c]			
S	≤0.03–8	2	4
IR	2–>32	4	>32
HR	>32	>32	>32
Cefaclor[c]			
S	0.06–16	1	4
IR	0.5–>32	8	>32
HR	16–>32	>32	>32
Cefetamet[c]			
S	0.12–16	2	8
IR	1–>32	16	>32
HR	16–32	>32	>32
Cefadroxil[c]			
S	0.12–16	2	8
IR	1–>32	16	>32
HR	>32	>32	>32
Cephalexin[c]			
S	0.12–16	4	8
IR	2–>32	>32	>32
HR	>32	>32	>32
Ceftibuten[c]			
S	0.25–>32	16	>32
IR	0.5–>32	>32	>32
HR	>32	>32	>32

[a] S (n = 272), susceptible to penicillin (MIC, ≤0.12 μg/ml); IR (n = 101), intermediately resistant to penicillin (MIC, 0.25 to 2 μg/ml); HR (n = 37), highly resistant to penicillin (MIC, ≥4 μg/ml).

[b] 50% and 90%, MICs at which 50 and 90% of the isolates are inhibited, respectively.

[c] Only 120 strains were studied (70 S, 25 IR, 25 HR).

imipenem, followed by cefpirome, FK-037, cefditoren, cefotaxime, ceftriaxone, and cefepime. However, MICs of ≥2 μl/ml of these cephalosporins were common among highly penicillin-resistant strains, and this could have therapeutic implications. These findings clearly indicate the need to determine the antibiotic susceptibilities of imipenem and extended-spectrum cephalosporins in all significant viridans group streptococcal isolates.

ACKNOWLEDGMENTS

This work was supported by grant 93/1196 from the Fondo de Investigaciones Sanitarias de la Seguridad Social de España and by a grant from the Fundació August Pi i Sunyer 1993–94 (Ciutat Sanitària i Universitària de Bellvitge).

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