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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 = ceftroxime > ceprozil = 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 125 µg/ml; cephalexin, 0.015 to 512 µg/ml; ceftroxil, 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 2 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 = ceftroxil >> 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...
Among 198 resistant isolates (i.e., 56% of the total), roughly three of four (i.e., 43% of the total) were of intermediate resistance and 17% had high-level resistance (8). Morerecently, 21% revealed intermediate 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 1. In vitro activities of selected β-lactam antimicrobial agents versus 352 blood culture isolates of viridans group streptococci

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>No. of isolates for which the MIC (μg/ml) is as follows:</th>
<th>% Resistant (breakpoint)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤0.008</td>
<td>0.015</td>
</tr>
<tr>
<td>Penicillin</td>
<td>8 (2)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>16 (5)</td>
<td>37 (15)</td>
</tr>
<tr>
<td>Cephalaxin</td>
<td>2 (0.6)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Cefprozil</td>
<td>2 (0.6)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>1 (0.3)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Cepfodoxime</td>
<td>7 (2)</td>
<td>13 (6)</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>2 (0.6)</td>
<td>3 (1)</td>
</tr>
</tbody>
</table>

* 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 cephalaxin, cefprozil, cefuroxime, and cefpodoxime.

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

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>No. (cumulative %) of isolates for which the MIC (μg/ml) is as follows:</th>
<th>% Resistant (breakpoint)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤0.008</td>
<td>0.015</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>4 (1)</td>
<td>31 (10)</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>1 (0.3)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td>1 (0.3)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>2 (1)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>3 (1)</td>
<td>50 (15)</td>
</tr>
<tr>
<td>Cepfodoxime</td>
<td>3 (1)</td>
<td>50 (15)</td>
</tr>
<tr>
<td>Rp 59500</td>
<td>1 (0.3)</td>
<td>1 (0.6)</td>
</tr>
</tbody>
</table>
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 against viridans group streptococci. The cephalosporine breakpoint of $\geq 2$ mg/ml was applied to cephalexin, cefprozil, cefuroxime, and cefpodoxime. The breakpoints for amoxicillin and TMP-SMX were those advocated by NCCLS for tests with penicillin, ceftriaxone, erythromycin, tetracycline, chloramphenicol, and ofloxacin versus viridans group streptococci. The cephalosporine breakpoint of $\geq 2$ mg/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.

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### REFERENCES


