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Activities of Potential Therapeutic and Prophylactic Antibiotics against Blood Culture Isolates of Viridans Group Streptococci from Neutropenic Patients Receiving Ciprofloxacin

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All 47 sequential blood culture isolates of viridans group streptococci obtained from febrile neutropenic patients receiving quinolone prophylaxis were susceptible to vancomycin, teicoplanin, and imipenem. Resistance to benzylpenicillin (MIC for 50% of isolates [MIC_{50}], 0.125 μg/ml) and ceftazidime (MIC_{50}, 4 μg/ml) was common. Most isolates were susceptible to amoxicillin, co-amoxiclav (amoxicillin-clavulanic acid at a 2:1 ratio by weight), azlocillin, clarithromycin, and erythromycin, with azithromycin showing comparable activity. The MIC_{90} of sparfloxacin was 1 μg/ml; those for ciprofloxacin and ofloxacin were >16 and 16 μg/ml, respectively.

Viridans group streptococci (other than pneumococci and enterococci) are now recognized as a major cause of infection in neutropenic patients (10). Although responsible for many infections in patients receiving quinolone prophylaxis (13), they are also a major cause of fever in patients not receiving prophylaxis (22). They can cause septicemic shock, adult respiratory distress syndrome (3, 7, 23), and appreciable mortality (10, 22). The potential consequences of infection with viridans group streptococci make prophylaxis desirable and require that initial empirical therapy for fever during neutropenia has activity against them. However, resistance to some β-lactam antibiotics may be common (21, 24), and prophylaxis with macrolides may not be effective (2, 25). Susceptibility tests on 286 isolates (mostly oropharyngeal) have shown quinolone (ofloxacin, ciprofloxacin, and norfloxacin)-resistant streptococci to be common isolates in patients receiving prophylactic ofloxacin (11).

We have assessed the in vitro antibiotic susceptibility of consecutive blood isolates from episodes of fever caused by viridans group streptococci in 47 neutropenic patients over a 2-year period. All patients were receiving oral antibacterial prophylaxis with ciprofloxacin at 500 mg twice a day and colistin at 1.5 MU twice a day. Ceftazidime and vancomycin were used for initial empirical therapy, with the subsequent addition of amikacin and amphotericin B in patients who did not respond. Blood culture isolates were stored at −70°C with the Protect bead system (Technical Service Consultants, Bury, Lancashire, United Kingdom). Identification to the species level was carried out according to the scheme described by Beighton et al. (1) to accommodate the recent taxonomic changes within the viridans group streptococci (1, 12). Isolates were also characterized with the API 20S system (bioMerieux, La Balme les Grottes, France) (equivalent to the Rapid Strep System; Analytab Products, Plainview, N.Y.). The results are shown in Table 1. MICs were determined according to British Society for Antimicrobial Chemotherapy (BSAC) guidelines (26). MICs of antibiotics were assessed with doubling dilutions in Iso-Sensitest agar (Oxoid, Basingstoke, United Kingdom) supplemented with 5% lysed sheep blood after overnight incubation for 18 h at 37°C in air. An inoculum of 10^4 CFU per spot (10^7 CFU/ml) was used. Each antibiotic was assessed in a single batch. The following antibiotics were kindly supplied as gifts by their manufacturers (all in the United Kingdom): amoxicillin and clavulanic acid (SmithKline Beecham, Weybridge, Surrey), azlocillin (Bayer UK, Newbury, Berkshire), benzylpenicillin (Glaxo Laboratories, Greenford, Middlesex), ceftazidime (Glaxo), imipenem (Merck Sharp & Dohme, Alton, Hampshire), azithromycin (Pfizer, Sandwich, Kent), clarithromycin (Abbott Laboratories, Maidenhead, Berkshire), erythromycin (Abbott), ciprofloxacin (Bayer UK), ofloxacin (Roussel Laboratories, Uxbridge, Middlesex), sparfloxacin (Rhone-Poulenc Rorer, Dagenham, Essex), teicoplanin (Marion Merrell Dow Ltd., Uxbridge, Middlesex), and vancomycin (Eli Lilly, Basingstoke, Hampshire). Co-amoxiclav consisted of amoxicillin and clavulanic acid in a 2:1 ratio by weight. *Escherichia coli* NCTC 10418 and *Staphylococcus aureus* NCTC 6571 were used as control organisms.

Synergy was assessed with doubling dilutions of amikacin and azlocillin for 17 isolates. Resistance to amikacin (MIC for 50% of isolates [MIC_{50}], 128 μg/ml) was common, and synergy was generally absent. Fractional inhibitory concentration indices were <0.5, <0.7, and >1.0 for two, six, and nine isolates, respectively.

MICs are shown in Table 2. On the basis of National Committee for Clinical Laboratory Standards (NCCLS) criteria (14) (the values are given for comparison only, as the BSAC methodology [26] used in this study differs from NCCLS methodology [15]), 61.7% of isolates were highly susceptible to benzylpenicillin (MIC, <0.25 μg/ml), with

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TABLE 1. Identification of viridans group streptococci isolated

Species (no. of isolates)[a]	Nomenclature with API 20S (no. of isolates)
Streptococcus oralis (39)	*S. mitis* (22), *S. sanguis* II (14), *Streptococcus* spp. (3)
Streptococcus mitis (5)	*S. sanguis* II (3), *S. salivarius* (1), *S. mitis* (1)
Streptococcus parasanguis (1)	*S. sanguis* II (1)
Streptococcus spp. (2)	*S. mitis* (2)

[a] Identified according to Beighton et al. (1).

21.3% showing moderate susceptibility (MIC, 0.25 to 2 μg/ml), and 17% were resistant (MIC, >2 μg/ml). For ceftazidime, 66% of isolates were fully susceptible (MIC, <16 μg/ml) and 23.4% were resistant (MIC, >16 μg/ml). For erythromycin, 8.5% showed intermediate susceptibility (MIC, 1 to 4 μg/ml) and the remainder were fully susceptible. All isolates were susceptible to imipenem and vancomycin. Identification to the species level, by either new or old taxonomies, did not predict antimicrobial susceptibility.

While oral vancomycin has proved to be effective as prophylaxis against viridans group streptococcal infections (2), the emergence of highly resistant gram-positive organisms (9) underlines the danger in using what may be the only effective class of antibiotics for routine prophylaxis. Intravenous benzylpenicillin may be effective (7), but even 4 years ago, 10 to 20% of isolates showed resistance (24). As only 61.7% of our isolates were fully susceptible to benzylpenicillin, it will not be useful as prophylaxis in our center. The development of such resistance will limit the use of quinolone-oral penicillin regimens currently being evaluated (6). The addition of a low dose of erythromycin to ciprofloxacin in a prophylactic regimen has not shown clinical benefit (25). However, Rozenberg-Arska et al. have shown that a short course of roxithromycin, started just before the period of maximum risk, is effective (19). In our study, erythromycin showed good activity, but resistant organisms may emerge rapidly (8). While azithromycin and clarithromycin both showed good activity, two isolates (for which the erythromycin MIC was 4 μg/ml) were highly resistant. Both isolates were also penicillin resistant (MIC, 8 μg/ml). The activities of clarithromycin and azithromycin against *Toxoplasma gondii* and atypical mycobacteria make them particularly interesting candidates as prophylactic agents for selected groups of patients.

While the currently available quinolones are effective as prophylaxis against coliforms and *S. aureus* (16), most other gram-positive cocci are either intrinsically resistant or gain resistance easily. The clinical utility of quinolones as prophylaxis for *S. aureus* may be a short-term benefit, limited by the emergence of quinolone-resistant organisms (20), as has occurred with coagulase-negative staphylococci (17). Ofloxacin was little more effective than ciprofloxacin in our study, with the MICs for almost all the isolates being between 2 and 8 μg/ml. Sparfloxacin offers the promise of increased activity against gram-positive cocci, although the MICs were 16 μg/ml for one isolate and 4 μg/ml for two isolates. The most resistant isolate was also resistant to β-lactam agents other than imipenem.

The frequency of resistance or reduced susceptibility to amoxicillin and benzylpenicillin in this study makes these agents unsuitable prophylactic agents. Benzylpenicillin had a bimodal distribution of susceptibilities: 32 isolates for which the MIC_{50} was 0.06 (range, 0.016 to 0.25) and 15 isolates for which the MIC_{50} was 4 μg/ml (range, 0.5 to 16). As expected, the addition of a β-lactamase inhibitor, clavulanic acid, to amoxicillin had no effect. For the 13 isolates for which the benzylpenicillin MICs were highest, the imipenem and ceftazidime MICs were also highest.

Some studies with patient groups not receiving quinolone prophylaxis suggest that glycopeptides need not be part of initial empirical therapy (4, 8). A higher proportion of episodes in patients receiving effective gram-negative bacterial prophylaxis will be due to viridans group streptococci (13) and, given their potential to cause fulminant disease, we consider that initial therapy must be active against viridans group streptococci. Ceftazidime and other β-lactams will not

TABLE 2. Susceptibility of 47 blood culture isolates of viridans group streptococci

Drug	MIC (μg/ml)			Breakpoint (μg/ml)[a]	% Susceptible
	Range	50%	90%		
Amoxicillin[b]	0.008–8	0.03	2	1	88.9
Co-amoxiclav[b,c]	0.008–8	0.016	8	1	89
Azlocillin	0.008–16	0.25	8	8–16	87.2–95.7
Benzylpenicillin	0.016–16	0.125	4	0.125[d]	61.7
Ceftazidime	0.125–>64	4	>64	2 (8)[d,e]	44.7 (66)[e]
Imipenem	0.008–2	0.03	1	4[d]	100
Azithromycin	0.016–>64[f]	0.016	1		
Erythromycin	0.03–4[f]	0.03	0.5	0.5[d]	91.5
Clarithromycin	0.008–>64[f]	0.016	1	2–4	93.6–95.7
Teicoplanin	0.03–4	0.25	0.5	4	100
Vancomycin	0.125–2	0.5	1	4[d]	100
Ciprofloxacin	1–>16	8	>16	1 (4)[d,e]	4.3 (23.4)[e]
Ofloxacin	0.5–>16	8	16	2 (8)[e]	4.3 (87.2)[e]
Sparfloxacin	0.25–16	1	2		

[a] From the BSAC Working Party report (26), except for the following: azithromycin—not applicable, azlocillin—estimated, and clarithromycin (18) and sparfloxacin—not available.

[b] Forty five isolates were tested.

[c] Susceptibilities are for the amoxicillin component.

[d] These breakpoints are numerically the same as those used to define susceptible isolates under NCCLS criteria (14) (see the text). The NCCLS breakpoint for ciprofloxacin is 1 μg/ml, and that for ceftazidime is 8 μg/ml.

[e] High breakpoints and corresponding percent susceptibilities are in parentheses.

[f] For two isolates, the azithromycin MIC was >64 μg/ml, the erythromycin MIC was 4 μg/ml, and the clarithromycin MICs were 32 and >64 μg/ml.

be useful unless a glycopeptide is also used. Teicoplanin and vancomycin had similar spectra of activity, and relative susceptibilities correlated well. As noted previously, imipenem is the most active β-lactam antibiotic (against viridans group streptococci) (24) and may be an alternative to β-lactam–glycopeptide combinations.

In conclusion, we have presented in vitro data to support the inclusion of either carbapenems or glycopeptides in initial empirical therapy for patient groups receiving prophylaxis with quinolones. Comparative trials with macrolide-quinolone combinations as prophylaxis are needed. However, the new generation of quinolones may offer similar in vitro efficacy (5), which might translate into simple but effective regimens.

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