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Nationwide German Multicenter Study on the Prevalence of Antibiotic Resistance in Streptococcal Blood Isolates from Neutropenic Patients and Comparative In Vitro Activities of Quinupristin-Dalfopristin and Eight Other Antimicrobials

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In a prospective multicenter study (1996 to 1999), 156 episodes of bacteremic streptococcal infections of neutropenic patients were evaluated. *Streptococcus oralis* (26.3%), *S. pneumoniae* (26.3%), *S. agalactiae* (11.5%), *S. mitis* (9%), and *S. pyogenes* (5.8%) were the predominant species. Four strains (2.6%) were found to be intermediately resistant to penicillin. One strain (0.6%) was found to be highly resistant to penicillin (MIC, 8 mg/liter). Reduced susceptibility to penicillin was detected among *S. oralis* (14.6%), *S. mitis* (7.1%), and *S. pneumoniae* (4.9%) isolates but was not recorded among *S. agalactiae* and *S. pyogenes*. Resistance rates and intermediate resistance rates for other antimicrobials were as follows (all species): amoxicillin, 1.3 and 3.2%; erythromycin, 16 and 2.6%; clindamycin, 5.8 and 0%; ciprofloxacin, 1.9 and 7.7%. Quinupristin-dalfopristin showed good in vitro activity against most streptococcal isolates (MIC at which 50% of the isolates were inhibited [MIC_{50}], 0.5 mg/liter; MIC_{90}, 1 mg/liter, MIC range, 0.25 to 4 mg/liter).

Bacterial infections represent life-threatening complications in patients with neutropenia, as has been observed in clinical trials evaluating febrile episodes in this patient group (3). During the past two decades, a trend towards an increasing number of gram-positive infections, in particular those caused by staphylococci and streptococci, has been observed worldwide (10). Various hypotheses for this trend have been elaborated, but the causes of this phenomenon still remain unclear.

Among the streptococcal species, the viridans group streptococci may be the most important pathogens causing bacteremia and sepsis in neutropenic patients (7). Until the 1980s, viridans group streptococci were considered to be uniformly susceptible to β-lactam antibiotics, but resistance spread rapidly in the 1990s. In a recent study on the antimicrobial susceptibilities of viridans group streptococci isolated from blood samples of neutropenic cancer patients in the Cologne area of Germany, only 81 and 74% of *Streptococcus mitis* and *Streptococcus oralis* strains, respectively, were susceptible to penicillin

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G (24). In addition, one *S. mitis* strain for which the penicillin MIC was 64 mg/liter has recently been isolated in Germany (8).

Quinupristin-dalfopristin is comprised of quinupristin (a type B streptogramin) and dalfopristin (a type A streptogramin) in a ratio of 30:70. It has a focused spectrum of in vitro activity against gram-positive cocci, mainly staphylococci (6, 20). In addition, preliminary studies have documented a reasonable activity of this antibiotic against viridans group streptococci and pneumococci including macrolide-resistant isolates (18). The aims of the present study were (i) to evaluate the prevalence of antibiotic resistance in streptococcal blood culture isolates in neutropenic patients and (ii) to compare the in vitro activity of quinupristin-dalfopristin with that of eight other antibiotics.

MATERIALS AND METHODS

Study design. Twenty-one microbiological laboratories serving university hospitals throughout Germany participated in this study. Each was requested to include all consecutive blood culture isolates from neutropenic patients with suspected streptococcal infections. Isolates were included from monomicrobial blood stream infections of patients with a white blood cell count of ≤1,000 cells/μl. The study design has been described in detail elsewhere (22).

Microbiological investigations. Streptococcal isolates were identified on the basis of their typical Gram stain and hemolysis on sheep blood agar. β-Hemolytic isolates were further identified by Lancefield grouping, using a commercially available agglutination technique (Slidex Streptokit; BioMérieux, Marcy-l'Etoile, France). *Streptococcus pyogenes* isolates were further identified by means of the pyrrolidonyl-arylamidase test. For further identification of *Streptococcus agalactiae* strains, the CAMP test was applied. For identification of the non-β-hemolytic isolates, the optochin test, bile solubility test, and bile esculin test were used. *Streptococcus pneumoniae* isolates were further confirmed with Neufeld's Quellung reaction. *Abiotrophia adiacens* was identified by testing for satelliting behavior. Viridans group streptococci and *Streptococcus bovis* were identified to species level with the Rapid ID 32 Strep system (BioMérieux) following the manufacturer's instructions. For some streptococcal strains without a clear-cut identification, the ability to produce leucine aminopeptidase and growth in broth containing 6.5% NaCl were used as identification criteria. One *Leuconostoc* sp. isolate was characterized by vancomycin resistance, the ability to produce gas from glucose in Mann Rogosa Sharpe broth, growth characteristics at 10 and 45°C, and a negative motility reaction.

Susceptibility testing. The antimicrobial susceptibilities of strains were determined by the microbroth dilution method as recommended by the National Committee for Clinical Laboratory Standards (NCCLS) (13). MICs were recorded for penicillin G, amoxicillin, erythromycin, clindamycin, vancomycin, teicoplanin, ciprofloxacin, gentamicin (high-level resistance), and quinupristin-dalfopristin, using commercially manufactured plates containing the antibiotics (Micronaut-S; Merlin Diagnostics, Bornheim, Germany) and cation-adjusted Mueller-Hinton broth (Oxoid, Wesel, Germany) containing 5% lysed horse blood (Oxoid).

Two macrolide-resistant *S. pyogenes* isolates were further characterized for underlying resistance mechanisms by means of a double-disk diffusion test with erythromycin and clindamycin disks. High-level gentamicin resistance (HLGR) was tested at a concentration of 500 mg/liter. Plates were read after incubation at 35°C for 20 to 24 h in ambient air. *S. pneumoniae* ATCC 49619 was used as a control strain. Isolates were stored at −70°C on porous beads (Microbank; Mast diagnostics, Rheinfeld, Germany) pending further use.

Typing of strains. Pneumococcal strains were serotyped by Neufeld's Quellung reaction using type and factor sera provided by the Statens Serum Institut, Copenhagen, Denmark. *S. pyogenes* strains were genotyped using a modified protocol of *emm* typing previously described by Podbielski et al. (16). In brief, for amplification of *emm* genes primers with the following sequences were designed: 5′ATA AGG AGC ATA AAA ATG GCT 3′ (all M forward) and 5′ AGC TTA GTT TTC TTC TTT GCG 3′ (all M reverse). Sequencing was performed with the ABI-Prism 310 genetic analyzer (Perkin-Elmer, Weiterstadt, Germany) according to the manufacturer's instructions. Similarity searching was performed using the N-terminal hypervariable region of the M gene according to Altschul et al. (1), based on the latest information available on the Centers for Disease Control and Prevention (Atlanta, Ga.) website (htpp://www.cdc.gov/ncidod/biotech/strep/strains/emmtypes.html). *S. pyogenes* CS101 (M type 49) was used as a reference strain.

Group B streptococci were serotyped by using type-specific rabbit antisera, kindly provided by P. Ferrieri (University of Minnesota, Minneapolis) and by R. Lütticken, and HCl extracts of group B streptococci in a double immunodiffusion test. Prototype stains (P. Ferrieri, University of Minnesota, Minneapolis) were used as reference strains.

RESULTS

A total of 156 streptococcal isolates were collected from March 1996 though February 1999 from neutropenic patients with bacteremia. Isolates were identified as *S. oralis* (n = 41, 26.3%), *S. pneumoniae* (n = 41, 26.3%), *S. agalactiae* (n = 18, 11.5%), *S. mitis* (n = 14, 9%), *S. pyogenes* (n = 11, 7.1%), *S. anginosus* (n = 7, 4.5%), *S. bovis* (n = 6, 3.8%), *S. salivarius* (n = 6, 3.8%), *S. dysgalactiae* subsp. *equisimilis* (Lancefield group G) (n = 3, 1.9%), *S. constellatus* (n = 2, 1.3%), *S. sanguis* (n = 2, 1.3%), *S. vestibularis* (n = 2, 1.3%), *Gemella morbillorum* (n = 1, 0.6%), *Leuconostoc* sp. (n = 1, 0.6%), and *A. adiacens* (n = 1, 0.6%). The majority of patients were male (62.4%); the mean age was 44 years (range, 1 to 88 years). The highest number of cases was identified in the age groups 51 to 60 years (27 cases), more than 70 years (23 cases), and 1 to 10 years (22 cases). The mean duration of hospitalization before a blood culture was drawn was 2.6 days (range, 1 to 6 days).

Data on antimicrobial susceptibility of all strains tested as well as on those of the four most prevalent species (*S. oralis, S. pneumoniae, S. agalactiae*, and *S. mitis*) are presented in Table 1. Erythromycin resistance was widespread among the streptococcal isolates (the MIC at which 50% of the isolates tested were inhibited [MIC_{50}] was ≤0.25 mg/liter; the MIC_{90} was 2 mg/liter; the MIC ranged from ≤0.25 to ≥32 mg/liter), while 2.6% of all isolates were found to be intermediately resistant to erythromycin, and 16% were found to be erythromycin resistant. Sixteen of the 32 erythromycin-resistant isolates (MIC ≥ 1 mg/liter) showed resistance to erythromycin and susceptibility to clindamycin (21). Sixteen isolates were found to be resistant to both erythromycin and clindamycin (macrolide-lincosamide-streptogramin B [MLS_B] type of resistance). Quinupristin-dalfopristin showed good in vitro activity against streptococcal isolates (MIC_{50}, 0.5 mg/liter; MIC_{90}, 1 mg/liter; MIC range, 0.25 to 4 mg/liter). Reduced susceptibility to quinupristin-dalfopristin (MIC ≥ 2 mg/liter) was seen predominantly in *S. bovis* (four of six *S. bovis* isolates) and *S. anginosus* (three of six isolates). In total, 6.4% of all streptococcal isolates were found to be intermediately resistant to quinupristin dalfopristin, and 1.3% were found to be quinupristin resistant when the breakpoints issued by the NCCLS for groups A and B streptococci were applied to all streptococci. Quinupristin-dalfopristin remained active (MIC ≤ 1 mg/liter) against 19 of 25 macrolide-resistant isolates and was more active against erythromycin-resistant and clindamycin-resistant strains (MIC range, 0.5 to 2 mg/liter; MIC_{50}, 0.5 mg/liter) than against erythromycin-resistant and clindamycin-susceptible strains (MIC range, 0.5 to 4 mg/liter; MIC_{50}, 2 mg/liter).

The double-disk diffusion test used with erythromycin-resistant isolates showed one strain to have a constitutive MLS_B phenotype and one strain to have an inducible MLS_B phenotype. HLGR was observed in 18.6% of the 156 isolates but differed widely among species (*S. oralis*, 17.1%; *S. agalactiae*, 83.3%; and *S. mitis*, 7.1%). Among *S. pyogenes* (n = 9) isolates, the following *emm* types were detected: *emm* 28 (two strains)

TABLE 1. MIC range, MIC_{50}, MIC_{90}, and resistance rates of 156 streptococcal isolates from neutropenic patients in Germany, 1996 to 1999

Species (no. of isolates)	Antibiotic[a]	MIC (mg/liter)			% I[b]	% R[b]
		Range	50%	90%		
All (156)	Pencillin G	≤0.06–8	≤0.06	≤0.06	2.6	0.6
	Amoxicillin	≤0.125–8	≤0.125	≤0.25	3.2	1.3
	Erythromycin	≤0.25–≥32	≤0.25	4	2.6	16
	Clindamycin	≤0.25–≥32	≤0.25	≤0.25	0	5.8
	Vancomycin[c]	0.25–≥32	≤0.25	0.5	0	0.6
	Teicoplanin[c]	0.25–16	≤0.25	≤0.25	0	0.6
	Ciprofloxacin[d]	0.25–32	0.5	2	7.7	1.9
	Q-D[e]	0.25–4	0.5	1	6.4	1.3
S. oralis (41)	Penicillin	≤0.06–2	≤0.06	0.25	14.6	0.0
	Amoxicillin	≤0.125–8	0.25	0.25	7.3	2.4
	Erythromycin	≤0.25–≥32	≤0.25	4	4.9	29.3
	Clindamycin	≤0.25–≥32	≤0.25	≤0.25	0	7.3
	Vancomycin[c]	0.25–1	1	1	0	0
	Teicoplanin[c]	0.25–0.5	≤0.25	≤0.25	0	0
	Ciprofloxacin[d]	0.25–32	2	4	24.4	4.9
	Q-D	0.25–4	1	1	4.9	0
S. pneumoniae (41)	Penicillin G	≤0.06–0.25	≤0.06	≤0.06	4.9	0.0
	Amoxicillin	≤0.125	≤0.125	≤0.125	0.0	0.0
	Erythromycin	≤0.25–4	≤0.25	≤0.25	2.4	2.4
	Clindamycin	≤0.25	≤0.25	≤0.25	0.0	0.0
	Vancomycin[c]	0.25–0.5	≤0.25	≤0.25	0.0	0.0
	Teicoplanin[c]	≤0.25	≤0.25	≤0.25	0.0	0.0
	Ciprofloxacin[d]	0.25–2	0.5	1	0.0	0.0
	Q-D	0.25–4	0.5	1	0.0	0.0
S. agalactiae (18)	Penicillin G	≤0.06	≤0.06	0.125	0.0	0.0
	Amoxicillin	≤0.125–0.5	≤0.25	≤0.25	0.0	0.0
	Erythromycin	≤0.25–≥32	≤0.25	4	5.6	11.1
	Clindamycin	≤0.25–≥32	≤0.25	≤0.5	0.0	5.6
	Vancomycin[c]	≤0.25–0.5	0.5	0.5	0.0	0.0
	Teicoplanin[c]	≤0.25	≤0.25	≤0.25	0.0	0.0
	Ciprofloxacin[d]	0.25–2	2	2	0	0.0
	Q-D	0.25–0.5	0.25	0.5	0.0	0.0
S. mitis (14)	Penicillin	≤0.06–8	≤0.06	≤0.06	0	7.1
	Amoxicillin	≤0.125–8	≤0.125	0.5	7.1	7.1
	Erythromycin	≤0.25–≥32	≤0.25	8	0.0	21.4
	Clindamycin	≤0.25–≥32	≤0.25	≤0.25	0.0	7.1
	Vancomycin[c]	0.25–1	0.5	0.5	0.0	0.0
	Teicoplanin[c]	0.25	≤0.25	≤0.25	0.0	0.0
	Ciprofloxacin[d]	0.25–2	1	2	0.0	0.0
	Q-D	0.25–4	1	2	14.3	0.0

[a] For data on HLGR, see the text.

[b] The following breakpoints for intermediate resistance (I) and resistance (R) according to NCCLS (13) were used: penicillin G (for *S. pneumoniae*), 0.1 to 1 and ≥2 mg/liter; penicillin G (for *Streptococcus* spp. other than *S. pneumoniae*), 0.25 to 2 and ≥4 mg/liter; amoxicillin (*S. pneumoniae*), 4 and ≥8 mg/liter; amoxicillin (for *Streptococcus* spp. other than *S. pneumoniae*), 0.5 to 4 and ≥8 mg/liter; erythromycin, 0.5 and ≥1 mg/liter; clindamycin, 0.5 and ≥1 mg/liter; ofloxacin, 4 and ≥8 mg/liter; quinupristin-dalfopristin, 2 and ≥4 mg/liter.

[c] All strains with vancomycin or teicoplanin MICs of ≤1 mg/liter were deemed to be susceptible.

[d] Ofloxacin breakpoints were used for ciprofloxacin because ciprofloxacin breakpoints are not available.

[e] Q-D, quinupristin-dalfopristin.

and *emm* 1, *emm* 3, *emm* 4, *emm* 11, *emm* 49, *emm* 75, and *emm* 77/27L (one strain each). Among pneumococcal strains (n = 41), 23 different serotypes were observed: 12F (12.2%), 6A (9.8%), 19F (9.8%), 23F (7.3%), 1, 4, 6B, 8, 18C, 33F (two strains [4.9%] each), and 3, 7F, 9N, 9V, 10A, 11A, 12B, 18F, 19A, 20, 23A, 24F, and 33C (one strain [2.4%] each). Among the *S. agalactiae* isolates (n = 18), 15 strains were serotyped. The following types were recorded: type Ib (five strains), type II (two strains), and type III (six strains). Two strains (−/R) were nontypeable with polysaccharide antisera. The R-protein antigen was detected in four of the six serotype III strains (III/R).

DISCUSSION

Streptococci are considered to be frequent causes of infection in immunocompromised patients, particularly after tissue transplantation, and in neutropenic cancer patients (2, 7, 14). This problem is exacerbated by the emerging resistance of streptococci to antimicrobial agents commonly used for empirical and prophylactic treatments in neutropenic patients. The increasing resistance of viridans group streptococci to β-lactam antibiotics has been documented in neutropenic cancer patients by various investigators (4, 12). The incidence of resistance has been associated with previous use of β-lactams and varies greatly among different institutions (2).

Overall, the findings of the present multicenter study are comparable with those of a study confined to viridans group streptococci isolated from blood samples of neutropenic cancer patients in the Cologne region of Germany (24). The authors of the study analyzed 50 episodes of bacteremia and also found high-level penicillin resistance in only one streptococcal isolate. Intermediate penicillin resistance was noted in 11 isolates (19%). Resistance to quinupristin-dalfopristin was not recorded among the isolates in the Cologne area. However, the authors did not report on episodes of *S. bovis* bacteremia, which contributed to the relatively high level of quinupristin-dalfopristin resistance in the present study.

Pfaller et al. examined the species distribution and antimicrobial susceptibility profile of 295 streptococcal nosocomial bloodstream isolates at more than 30 U.S. medical centers (SCOPE National Surveillance Program). In that study, streptococci accounted for 5.9% of all nosocomial bloodstream isolates reported. The viridans group streptococci were the most frequently isolated streptococci (50.8%), followed by β-hemolytic streptococci (31.9%) and pneumococci (13.2%). The leading species responsible for infections by β-hemolytic streptococci was *S. agalactiae* (63%), followed by streptococci of serogroups A and G. These authors reported 14% of *S. pneumoniae* and 9.2% of viridans group streptococci to be resistant to penicillin (15). In the present study, *S. agalactiae* also ranks first among the β-hemolytic streptococci, but *S. pneumoniae* is recognized as causing bloodstream infection in neutropenic patients as frequently as *S. oralis*.

Kugler et al. recently reported three *Streptococcus* sp. strains to be resistant to quinupristin-dalfopristin (MICs at 3, 8, and 12 mg/liter) following referral as routine isolates in the SENTRY Antimicrobial Surveillance Program. All strains were also resistant to macrolides (erythromycin, azithromycin, clarithromycin), lincosamides (clindamycin), and fluoroquinolones. Patient histories indicated no prior use of MLS_B class antimicrobials for the *S. mitis* case, but the patient from whom the *S. pneumoniae* isolate originated had received prior treatment comprising erythromycin and clindamycin. The data of our study and the observations by Kugler et al. illustrate the existence of streptogramin-resistant isolates prior to the introduction of this antimicrobial class into human clinical practice (9).

Carratala et al. studied 260 episodes of bacteremia over a 6-year period in neutropenic cancer patients in a Spanish hospital. Fourteen of 23 episodes (57%) were caused by penicillin-

resistant viridans streptococcus (MIC range, 0.25 to 8 mg/liter) strains. Ten of the 14 penicillin-resistant strains (77%) were highly resistant to penicillin (MIC ≥ 4 mg/liter) (2). Penicillin-resistant oral streptococci constitute the genetic reservoir for β-lactam resistance in *S. pneumoniae*. Strains of *S. mitis* for which the penicillin MIC was unusually high (64 mg/liter) have recently been isolated in Germany from the throat culture of an asymptomatic child (8). Such strains were not seen among the 156 streptococcal isolates in the present investigation, but a strain for which a penicillin MIC was 8 mg/liter was documented.

The level of macrolide resistance of pneumococci documented by the present study (2.4%) is clearly lower than the 15 to 25% rate documented by ongoing nationwide surveillance studies of invasive disease in both children (23) and adults in the year 2000 (R. R. Reinert, unpublished data).

It is noteworthy that *S. agalactiae* is now found to be one of the streptococcal species predominantly responsible for bacteremia in neutropenic patients. We found a very high proportion of *S. agalactiae* isolates with HLGR. The data of our study indicate that this resistance mechanism may be widespread among *S. agalactiae* isolates, limiting the potential success of a β-lactam aminoglycoside combination in the treatment of *S. agalactiae* infections. In the present study, all streptococcal strains with the exception of one *Leuconostoc* isolate were susceptible to glycopeptides. Reduced susceptibility to glycopeptides has been only rarely observed in the genus *Streptococcus* (11). In addition, a superior in vitro activity of teicoplanin over vancomycin in streptococcal isolates was observed, confirming the results of the European Glycopeptide Susceptibility Survey of gram-positive bacteria (5).

The serotype distribution of pneumococcal strains in neutropenic patients differs widely from that generally observed in invasive disease in Germany, where serotypes 1, 14, 3, and 23F are predominant in adults (19). Serotype 12F, which was most often seen in the present study, is generally detected in less than 1% of cases of invasive pneumococcal disease in Germany (17, 19, 23). All serotype 12F strains were isolated at different institutions, indicating that an epidemiological relatedness of isolates is unlikely. In addition, some serotypes only rarely observed in Germany were responsible for infections in the present study, indicating that potentially less virulent strains may be responsible for infections in neutropenic patients. Consequently, the coverage rate of the 23-valent pneumococcal polysaccharide vaccine is lower in neutropenic patients (78%) than that normally observed in invasive pneumococcal disease in Germany (90%). The observation of an unusual serotype and *emm* type distribution has also been made among *S. agalactiae* and *S. pyogenes* isolates, but data for these two species should be interpreted with caution, as the number of isolates is relatively low.

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