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Antimicrobial Susceptibility Patterns of ß-Haemolytic and Viridans Group Streptococci: Report From the SENTRY Antimicrobial Surveillance Program (1997-2000)

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ABSTRACT

Objective: To determine susceptibility patterns of 15 antimicrobial agents tested against ß-haemolytic (ßhS) and viridans group (VgS) streptococci in 4 regions of the SENTRY Program: Asia-Pacific (AP), Europe (EU), Latin America (LA) and North America (NA).
Methods: Between January 1997 and December 2000, SENTRY Program monitors received 3,400 ßhS (n=2,248) and VgS (n=1,152) isolates from 4 geographic regions: AP (408), EU (777), LA (332) and NA (1,883). All isolates were tested by reference broth microdilution methods and interpreted using NCCLS criteria. Among the ßhS tested, 81.9% were either serogroup A (650) or B (1,190). The VgS were classified as unspeciated alpha-strept (512; 44%), *S. mitis* (254; 22%) and other speciated *Streptococcus* spp. (386; 34%). Seven quinolones, two ß-lactams, erythromycin (ER), clindamycin (CM), quinupristin/dalfopristin (Q/D), vancomycin (VA), teicoplanin (TP) and linezolid (LZ) were routinely tested.
Results: Rank order of susceptibility for ßhS was: ceftriaxone (CTX) = Q/D = VA = TP = LZ (100.0%) > gatifloxacin (GATI; 99.8%) = trovafloxacin (TROV; 99.8%) > levofloxacin (LEVO; 99.7%) > penicillin (PEN; 99.3%) > grepafloxacin (GREP; 97.4%) > CM (94.4%) > ER (85.5%). GATI, GREP and TROV all had the same MIC_{50} (0.25 µg/ml) and MIC_{90} (0.5 µg/ml) result against ßhS, while LEVO had MIC_{50} and MIC_{90} results that were two-fold higher. ER versus ßhS had the highest MIC_{90} value (2 µg/ml) and the lowest susceptibility across all regions (range, 81.4% in NA to 97.3% in LA). Among the VgS, susceptibility rank order was: VA = TP = LZ (100.0%) > Q/D (99.1%) > GATI = LEVO = TROVA (98.0%) > GREP (96.5%) > CTX (92.8%) > CM (90.3%) > PEN (68.6%) > ER (64.5%). VgS was 62.7, 68.1 and 57.8% susceptible to ER in AP, LA and NA, respectively.
Conclusions: Among ßhS, macrolide resistances have increased to 13.8% and CM resistance was 5.3%. These rates were two-fold greater in VgS with quinolone observed-resistant strains were observed at 0.6 - 1.3%. Similar to pneumococci, other streptococci have acquired resistances and require continued surveillance.

INTRODUCTION

Viridans group and ß-haemolytic streptococci are highly prevalent organisms among the normal flora of the oral cavity, gastrointestinal tract and female genital tract. For decades, the drug of choice to treat *Streptococcus pyogenes* has been penicillin and to date, this remains a useful therapeutic option. However, there have been some treatment failures using penicillin, most likely due to insufficient dosing regimens, tolerance to the drug, or drug hydrolysis by ß-lactamases produced by non-streptococcal species found in the upper airways.

Newer cephalosporins and macrolides are alternative agents, which can be utilized in the treatment of infections caused by streptococcal isolates, if the patient has an allergic reaction to penicillin. However, resistance to erythromycin among *S. pyogenes* isolates has been documented in many areas of the world. Macrolides, such as clarithromycin and azithromycin, are more stable and have improved pharmacokinetics, and require less frequent dosing than erythromycin.

Penicillin has also been the preferred choice for the treatment of infections caused by *Streptococcus agalactiae*. Roughly 10 to 35% of asymptomatic pregnant women carry *S. agalactiae* in their genital and gastrointestinal tracts. As a safe prophylactic treatment, macrolides are commonly administered to pregnant women suspected of colonization with *S. agalactiae*. However, an increase in macrolide-resistance among *S. agalactiae* has caused concern about the continued use of this drug class for prophylaxis.

Unlike ß-haemolytic strains, viridans group streptococci have demonstrated resistance to penicillins and other ß-lactams. This is cause for concern among neutropenic cancer patients as viridans group streptococci are one of the most common causes of bacteremia in this at risk population.

The purpose of this study was to gather the antimicrobial susceptibility patterns of ß-haemolytic and viridans group streptococci from various regions in the world utilizing the SENTRY Antimicrobial Surveillance Program and assess the role of a new des-fluoro(6) quinolone, BMS 284756.

MATERIALS AND METHODS

Between January 1997 and December 2000, 3,400 streptococcal isolates from more than 80 medical centers in four different geographical regions were forwarded to SENTRY Program monitors. Strains were collected from sites in Asia-Pacific (n =408), Europe (n = 777), Latin America (n =332), and North America (n = 1,833). ß-haemolytic species, accounted for two-thirds of all streptococci (2,248 isolates) of which nearly 82% were either *S. pyogenes* (serogroup A; n = 650 isolates) or *S. agalactiae* (serogroup B; n = 1,190 isolates). The remaining 1,152 streptococcal isolates included viridans group streptococci, generally referred to as α-haemolytic streptococci (44%). Among the viridans group streptococci, *Streptococcus mitis* (22%) represented the majority of the identified species.

Strains were isolated from significant bloodstream, lower respiratory tract, and skin and soft tissue infections. Cultures of isolates were transported to the SENTRY Program monitors in a transport medium. Referring laboratories provided species identification and/or serogroup confirmation of the isolates. If questionable colony morphology or an unusual antimicrobial susceptibility pattern was of concern, further identification confirmation was deemed necessary.

Isolates were tested using NCCLS reference broth microdilution methods and common reagent lots in all geographic regions. Each strain was tested against quinolones (BMS 284756, ciprofloxacin, gatifloxacin, grepafloxacin, levofloxacin, sparfloxacin, and trovafloxacin), penicillin, ceftriaxone, erythromycin, clindamycin, quinupristin/dalfopristin, vancomycin, teicoplanin, and linezolid. MIC values were interpreted using NCCLS M100-S12 guidelines. Quality control was performed using American Type Culture Collection (ATCC) strains including *Streptococcus pneumoniae* ATCC 49619, *Enterococcus faecalis* ATCC 29212, and *Staphylococcus aureus* ATCC 29213.

RESULTS

Antimicrobial activity of tested drugs against ß-haemolytic streptococci (Table 1)

- Rank order of susceptibility for those quinolones with NCCLS interpretative criteria was: gatifloxacin = levofloxacin = trovafloxacin (99.7 - 99.8%) > grepafloxacin (97.4%)
- Rank order of potency (MIC_{90}) was: BMS 284756 (0.12 µg/ml) > gatifloxacin = grepafloxacin = sparfloxacin = trovafloxacin (0.5 µg/ml) > ciprofloxacin = levofloxacin (1 µg/ml)
- Rank order of susceptibility versus the remaining eight antimicrobial agents was: ceftriaxone = linezolid = quinupristin/dalfopristin = teicoplanin = vancomycin (100.0%) > penicillin (99.3%) > clindamycin (94.4%) > erythromycin (85.5%)
- Quinupristin/dalfopristin, gatifloxacin, grepafloxacin, and trovafloxacin had MIC_{50} values of 0.25 µg/ml and MIC_{90} values of 0.5 µg/ml, while erythromycin appeared to be the least active with the highest recorded MIC_{90} (2 µg/ml) and a resistance rate of 13.8%

Antimicrobial activity of tested drugs against viridans group streptococci (Table 1)

- Rank order of susceptibility for those quinolones with NCCLS criteria was similar to that for ß-haemolytic streptococci: gatifloxacin = levofloxacin = trovafloxacin (98.0%) > grepafloxacin (96.5%)
- Rank order of potency using MIC_{90} values was nearly identical to that for ß-haemolytic isolates: BMS 284756 (0.12 µg/ml) > gatifloxacin = grepafloxacin = trovafloxacin (0.5 µg/ml) > sparfloxacin (1 µg/ml) > levofloxacin (2 µg/ml) > ciprofloxacin (> 2 µg/ml)
- Rank order of susceptibilitiy for the remaining antimicrobial agents was: linezolid = teicoplanin = vancomycin (100.0%) > quinupristin/dalfopristin (99.1%) > ceftriaxone (92.8%) > clindamycin (90.3%) > penicillin (68.6%) > erythromycin (64.5%)
- Teicoplanin demonstrated excellent potency with MIC_{50} and MIC_{90} values of ≤ 0.12 µg/ml while quinupristin/dalfopristin and vancomycin demonstrated similar results to those seen against ß-haemolytic streptococci

Regional differences in susceptibility patterns

- Gatifloxacin and trovafloxacin had MIC_{90} values against ß-haemolytic streptococci of 0.25 µg/ml in the Asia-Pacific region and 0.5 µg/ml in Europe, Latin America, and North America. Grepafloxacin had the most variability in susceptibility rates ranging from 93.5% in Europe to 100.0% in Latin America (Table 2)
- Erythromycin had MIC_{90} values of 2 µg/ml and susceptibilities of 81.4 and 89.1% in North America and Asia-Pacific respectively, in contrast to Europe and Latin America where lower MIC_{90} values of 0.25 µg/ml and susceptibilities ranging from 90.3 to 97.3%, respectively were recorded (Table 2)
- For viridans group streptococci the M-phenotype (resistant to erythromycin and susceptible to clindamycin; (Table 3) was most often observed among macrolide-resistant strains in North American strains (81.5%) and was lowest in the Asia-Pacific region (57.1%)
- For ß-haemolytic streptococci, the M-phenotype was more often detected in Latin America (66.7%) and least isolated in Europe (41.2%). For both groups of streptococci (Tables 2 and 3), the M-phenotype was significantly more prevalent in the Americas compared to Asia-Pacific or Europe

CONCLUSIONS

- There were few notable differences in susceptibility patterns between regions for either ß-haemolytic or viridans group streptococci for most of the antimicrobials tested
- Erythromycin had the broadest range of susceptibility rates for ß-haemolytic streptococci (81.4%-97.3%) and for viridans group streptococci (57.8%-73.7%)
- BMS 284756 was the most active quinolone (MIC_{90}, 0.12 µg/ml) against both ß-haemolytic and viridans group streptococci
- Penicillin continues to be a very effective antimicrobial (99.3% susceptibility) versus ß-haemolytic streptococci as compared to only a 68.6% susceptibility rate versus viridans group streptococci
- For ß-haemolytic streptococci, the M-phenotype was more often detected in Latin America and least isolated in Europe. For both groups of streptococci, the M-phenotype was significantly more prevalent in the Americas compared to Asia-Pacific or Europe, where the constitutive resistance of the *erm*-type was greatest

Table 1. The in vitro potency of 15 antimicrobial agents tested against 3,400 isolates of ß-haemolytic and viridans group streptococci from the SENTRY Antimicrobial Surveillance Program worldwide (1997-2000).

	Organism (no. tested)			
	ß-haemolytic streptococci (2,248)		viridans gr. streptococci (1,152)	
Antimicrobial agent	$MIC_{50/90}$ (µg/ml)	% susc./resist.[a]	$MIC_{50/90}$ (µg/ml)	% susc./resist.[a]
BMS 284756	0.06/0.12	-	0.06/0.12	-
Ciprofloxacin	0.5/1	-	1/>2	-
Gatifloxacin	0.25/0.5	99.8/0.2	0.25/0.5	98.0/1.3
Grepafloxacin	0.25/0.5	97.4/0.2	0.25/0.5	96.5/0.6
Levofloxacin	0.5/1	99.7/0.2	1/2	98.0/1.3
Sparfloxacin	0.5/0.5	-	0.5/1	-
Trovafloxacin	0.25/0.5	99.8/0.2	0.12/0.5	98.0/1.3
Penicillin	0.03/0.12	99.3/-[b]	0.06/1	68.6/5.9
Ceftriaxone	≤0.25/≤0.25	100.0/-	0.25/1	92.8/4.2
Erythromycin	0.25/2	85.5/13.8	0.25/4	64.5/29.9
Clindamycin	≤0.06/0.12	94.4/5.3	≤0.06/0.25	90.3/9.1
Quinupristin/Dalfopristin	0.25/0.5	100.0/0.0	0.5/1	99.1/0.0
Vancomycin	0.5/0.5	100.0/-	0.5/1	100.0/-
Teicoplanin	≤0.12/0.25	100.0/-	≤0.12/≤0.12	100.0/-
Linezolid	1/1	100.0/-	1/1	100.0/-

a. Interpretive criteria of the NCCLS [2002].
b. A total of 0.7% of strains had a penicillin MIC of 0.25 µg/ml = non-susceptible.
- = no interpretive criteria are published by the NCCLS [2002].

Table 2. Regional variations in the potency and spectrum of 15 antimicrobial agents tested against 2,248 isolates of ß-haemolytic streptococci from the SENTRY Antimicrobial Surveillance Program worldwide (1997-2000).

	MIC_{90}/% susceptible[a] by region (no. tested):			
Antimicrobial agent	Asia-Pacific (257)	Europe (403)	Latin America (219)	North America (1,369)
BMS 284756	0.12/-[b]	0.12/-	0.12/-	0.12/-
Ciprofloxacin	1/-	1/-	1/-	1/-
Gatifloxacin	0.25/100.0	0.5/99.8	0.5/100.0	0.5/99.7
Grepafloxacin	0.25/97.2	0.5/93.5	0.25/100.0	0.5/98.6
Levofloxacin	1/99.4	1/99.7	1/100.0	1/99.7
Sparfloxacin	NT[b]	1/-	1/-	0.5/-
Trovafloxacin	0.25/100.0	0.5/100.0	0.5/100.0	0.5/99.7
Penicillin	0.06/99.6	0.06/99.0	0.06/100.0	0.12/99.2
Ceftriaxone	≤0.25/100.0	≤0.25/100.0	≤0.25/100.0	≤0.25/100.0
Erythromycin	2/89.1	0.25/90.3	0.25/97.3	2/81.4
Clindamycin	0.12/95.3	0.12/95.3	0.12/99.1	0.12/93.2
Quinupristin/Dalfopristin	0.5/100.0	1/100.0	0.5/100.0	0.5/100.0
Vancomycin	0.5/100.0	0.5/100.0	0.5/100.0	0.5/100.0
Teicoplanin	0.25/100.0	0.25/100.0	≤0.12/100.0	0.25/100.0
Linezolid	1/100.0	1/100.0	1/100.0	1/100.0

a. Susceptibility categories were assigned using NCCLS [2002] breakpoints.
b. NT = not tested and - = no criteria for this category published in the NCCLS [2002] standards.

Table 3. Regional variations in the potency and spectrum of 15 antimicrobial agents tested against 1,152 isolates of viridans group streptococci from the SENTRY Antimicrobial Surveillance Program worldwide (1997-2000).

	MIC_{90}/% susceptible by region (no. tested):[a]			
Antimicrobial agent	Asia-Pacific (151)	Europe (374)	Latin America (113)	North America (514)
BMS 284756	0.12/-[b]	0.12/-	0.12/-	0.12/-
Ciprofloxacin	>2/-	>2/-	>2/-	>2/-
Gatifloxacin	0.5/100.0	0.5/97.6	0.5/97.3	0.5/98.6
Grepafloxacin	0.25/100.0	0.5/96.7	0.5/93.9	0.5/96.2
Levofloxacin	2/100.0	2/97.0	2/97.3	2/98.4
Sparfloxacin	NT[b]	1/-	1/-	0.5/-
Trovafloxacin	0.25/100.0	0.5/98.7	0.5/98.7	0.5/97.1
Penicillin	1/69.3	2/70.1	2/69.0	1/67.3
Ceftriaxone	1/92.9	0.5/91.7	1/90.3	0.5/94.0
Erythromycin	>8/62.7	2/73.7	2/68.1	4/57.8
Clindamycin	>2/84.0	1/89.3	0.12/92.9	0.12/92.2
Quinupristin/Dalfopristin	1/96.0	1/99.7	1/99.1	1/99.6
Vancomycin	1/100.0	1/100.0	1/100.0	1/100.0
Teicoplanin	≤0.12/100.0	≤0.12/100.0	0.25/100.0	≤0.12/100.0
Linezolid	1/100.0	1/100.0	1/100.0	1/100.0

a. Susceptibility categories were assigned using NCCLS [2002] breakpoints.
b. NT = not tested and - = no criteria for this category published in the NCCLS [2002] standards.