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Activities of New Fluoroquinolones, Ketolides, and Other Antimicrobials against Blood Culture Isolates of Viridans Group Streptococci from across Canada, 2000

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The rates of nonsusceptibility to penicillin, erythromycin, and clindamycin of 191 blood culture isolates of viridans group streptococci collected from across Canada in 2000 were 36, 42, and 10%, respectively. Although 8% of the strains were resistant to ciprofloxacin (MIC ≥ 4 μg/ml), the MICs of gemifloxacin, BMS 284756, telithromycin, and ABT 773 at which 90% of the strains were inhibited were 0.06, 0.06, 0.12, and 0.03 μg/ml, respectively.

Viridans group streptococci (VGS) are a common cause of bacterial endocarditis and sepsis in immunocompromised patients. Increasing resistance to commonly used antimicrobials has complicated the management of patients with these conditions (2, 4, 5, 14). There has been a previous report on the prevalence of antimicrobial resistance in VGS collected from across Canada between 1995 and 1997 (2). The purpose of this study was to report data on the in vitro activities of newer fluoroquinolones, ketolides, linezolid, and other antimicrobials against blood culture isolates of VGS collected in 2000 from across Canada through an ongoing surveillance program and to compare the rates of resistance with those reported in the previous study.

In 2000, 191 blood culture isolates of VGS were collected from 27 clinical microbiology laboratories through the Canadian Bacterial Surveillance Network, an ongoing surveillance program consisting of private laboratories and laboratories in community- and university-affiliated hospitals from 9 of the 10 Canadian provinces. The isolates were sent to Mount Sinai Hospital, Toronto, Ontario, for susceptibility testing and, when indicated, species identification (2). Species identification was performed for isolates with decreased susceptibility to penicillin, erythromycin, ciprofloxacin, or two or more different classes of antimicrobials. Susceptibility testing was performed by broth microdilution in accordance with National Committee for Clinical Laboratory Standards (NCCLS) guidelines (11). The antimicrobials were obtained from their respective manufacturers. *Streptococcus pneumoniae* ATCC 49619 was used as a control organism. NCCLS MIC interpretive standards were used. For ciprofloxacin, MICs of ≥4 μg/ml were used to define the resistance category. PCR was used to detect the *erm* and *mef* genes in all isolates that were found to be nonsusceptible to erythromycin (MIC ≥ 0.5 μg/ml), as described previously (3). Cycling was carried out by using a Perkin-Elmer 9600 thermocycler with 5 μl of template (3) in a 25-μl reaction mixture as follows: initial denaturation at 94°C for 4 min followed by denaturation at 93°C for 30 s, annealing at 50°C for 30 s, and elongation at 72°C for 1 min for a total of 30 cycles. A final extension step was carried out at 72°C for 5 min. PCR products were resolved on 1% agarose gels.

The MICs of the various antimicrobials for the 191 VGS blood culture isolates are depicted in Table 1. As has been noted in other countries, relatively high rates of resistance to all of the antimicrobials tested, with the exception of the newer agents, were found (4, 5, 8, 13, 15, 18, 19, 21). In addition, we found that there had been increases in the rates of nonsusceptibility to penicillin, erythromycin, and clindamycin compared to those reported in a similar surveillance study carried out between 1995 and 1997, from 28 to 37, 29 to 42, and 4 to 10%, respectively (2). A total of 70 isolates (37%) were nonsusceptible to penicillin, of which 14 (7%) were resistant. Eighty-one isolates were nonsusceptible to erythromycin (MIC ≥ 0.5 μg/ml). The *erm* gene was detected in 13 isolates, and all of these were resistant to clindamycin (MIC range, 16 to ≥64 μg/ml). All 59 isolates in which the *mef* gene alone was detected were susceptible to clindamycin, and the erythromycin MICs for these isolates ranged from 0.5 to 8 μg/ml. By comparison, the erythromycin MICs for 12 of the 13 strains possessing *erm* were >64 μg/ml. A single strain (for which the erythromycin MIC was 8 μg/ml) harbored both the *erm* and *mef* genes. Neither the *erm* nor the *mef* gene was detected in eight isolates (for which the erythromycin MICs were 0.5 to >64 μg/ml). Linezolid, the

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† Members are listed in the Appendix.

TABLE 1. In vitro susceptibilities of 191 blood culture isolates of VGS collected in 2000 to selected antimicrobial agents

Antimicrobial agent	No. (cumulative %) of strains for which MIC (μg/ml) was:													
	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	≥64
Penicillin	27 (14)	0 (14)	32 (31)	32 (48)	30 (63)	24 (76)	15 (84)	7 (87)	10 (93)	10 (98)	2 (99)	2 (100)		
Ceftriaxone	ND[a]	ND	102 (53)	10 (59)	5 (61)	33 (76)	15 (86)	10 (92)	8 (96)	4 (98)	4 (100)			
Erythromycin	ND	ND	ND	ND	110 (58)	0 (58)	5 (60)	6 (63)	21 (74)	27 (88)	5 (91)	0 (91)	0 (91)	17 (100)
Clindamycin	ND	ND	ND	ND	ND	172 (90)	0 (90)	0 (90)	0 (90)	1 (91)	3 (92)	1 (93)	1 (93)	13 (100)
Doxycycline	ND	ND	ND	ND	ND	ND	ND	137 (72)	3 (73)	2 (74)	9 (79)	27 (93)	13 (100)	
TMP-SMX[b]	ND	ND	ND	ND	ND	105 (55)	29 (70)	24 (83)	12 (89)	13 (96)	7 (99)	0 (99)	0 (99)	1 (100)
Ciprofloxacin	ND	ND	ND	ND	0 (0)	5 (3)	43 (25)	88 (71)	39 (92)	9 (96)	3 (98)	3 (99)	0 (99)	1 (100)
Levofloxacin	ND	ND	ND	ND	0 (0)	7 (4)	49 (29)	103 (83)	24 (96)	4 (98)	3 (99)	1 (100)		
Gatifloxacin	ND	ND	0 (0)	2 (1)	44 (24)	104 (79)	35 (97)	2 (98)	2 (99)	2 (100)				
Moxifloxacin	ND	ND	2 (1)	52 (28)	93 (77)	37 (96)	3 (98)	3 (99)	1 (100)					
Gemifloxacin	34 (18)	61 (50)	56 (79)	32 (96)	2 (97)	4 (99)	2 (100)							
BMS 284756	2 (1)	14 (8)	69 (45)	87 (90)	12 (96)	3 (98)	1 (98)	3 (100)						
Linezolid	ND	ND	ND	ND	ND	0 (0)	20 (10)	146 (87)	24 (99)	1 (100)				
Telithromycin	ND	122 (64)	13 (71)	24 (83)	21 (94)	9 (99)	2 (100)							
ABT 773	ND	169 (89)	13 (95)	4 (97)	0 (97)	1 (98)	2 (99)	1 (99)	1 (100)					

[a] ND, not determined.
[b] TMP-SMX, trimethoprim-sulfamethoxazole at a 19:1 ratio.

first of the new class of oxazolidinone antibiotics, has been approved by the U.S. Food and Drug Administration for the treatment of infections associated with vancomycin-resistant *Enterococcus faecium*, hospital-acquired pneumonia, and complicated skin and skin structure infections, including cases of methicillin-resistant *Staphylococcus aureus* infection (22). For all of the isolates tested, linezolid MICs were ≤2 μg/ml.

Most published studies regarding the activity of the carbapenems to VGS are limited to imipenem, which has been found to be very active against these organisms (16, 18, 21). Currently the NCCLS includes only meropenem in its interpretive standards for *Streptococcus* spp. other than *S. pneumoniae* and provides breakpoints only for the susceptible category (≤0.5 μg/ml). An absence of resistant strains at the time the standards were established precluded the definition of intermediate and resistant categories (10). Marron et al. (7), however, found that for 20% of VGS strains isolated from the blood of neutropenic cancer patients in their hospital, the imipenem MICs were ≥1 μg/ml (MIC ranges of 1 to 2 μg/ml). In addition, for 9% of our isolates, the meropenem MICs were ≥1 μg/ml (MIC ranges of 1 to 4 μg/ml). Since it is recognized that the carbapenems may lose their potency in frozen microdilution susceptibility panels over time, we retested all isolates for which the meropenem MIC was >0.5 μg/ml with panels made on the same day (12, 20). There was complete concordance between both sets of results (data not shown). This emerging resistance of VGS to the carbapenems may challenge the concept of using meropenem monotherapy for febrile neutropenic patients (6).

The interpretive standards for VGS susceptibility to cefotaxime, ceftriaxone, and cefepime are ≤0.5, 1, and ≥2 μg/ml for susceptible, intermediate, and resistant, respectively (10). New interpretive standards of ≤1, 2, and ≥4 μg/ml for susceptible, intermediate, and resistant, respectively, have been implemented in the NCCLS guidelines for 2002 (11). For ceftriaxone, the numbers of intermediate and resistant isolates have decreased from 10 (5%) and 16 (8%) to 8 (4%) and 8 (4%), respectively (Table 1).

The rates of resistance to ciprofloxacin were 8% in both this study and a similar study carried out in Canada between 1995 and 1997 (2). For strains for which the ciprofloxacin MIC was ≥4 μg/ml, the levofloxacin MIC at which 50% of strains were inhibited (MIC_{50}) and MIC_{90} were 2 and 8 μg/ml, respectively. The MIC_{90}s of the other fluoroquinolones were at least fourfold lower (Table 2).

Identification at the species level was carried out for 123 resistant strains. The levels of antimicrobial activity against 118 strains belonging to the most prevalent species are shown in Table 3. *Streptococcus milleri* (4 strains) and *Streptococcus bovis* (1 strain) were not included in the table. There were no *Streptococcus mutans* organisms identified. The largest number of isolates (54%) were *Streptococcus mitis* isolates. Of the 16

TABLE 2. In vitro susceptibilities to fluoroquinolones of 16 blood culture isolates of VGS isolated from patients in 2000 for which the ciprofloxacin MIC was ≥4 μg/ml

Antimicrobial agent	No. (cumulative %) of strains for which MIC (μg/ml) was:													
	<0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	≥64
Ciprofloxacin	ND[a]	ND	ND	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	9 (56)	3 (75)	3 (94)	0 (94)	1 (100)
Levofloxacin	ND	ND	ND	ND	0 (0)	0 (0)	0 (0)	1 (6)	7 (50)	4 (75)	3 (94)	1 (100)		
Gatifloxacin	ND	ND	0 (0)	0 (0)	0 (0)	0 (0)	10 (62)	2 (75)	2 (88)	2 (100)				
Moxifloxacin	ND	ND	0 (0)	0 (0)	0 (0)	11 (69)	1 (75)	0 (75)	3 (94)	1 (100)				
Gemifloxacin	0 (0)	0 (0)	0 (0)	10 (63)	0 (63)	4 (88)	0 (88)	2 (100)						
BMS 284756	0 (0)	0 (0)	0 (0)	5 (31)	6 (69)	1 (75)	1 (81)	3 (100)						

[a] ND, not determined.

TABLE 3. Antimicrobial activities of various agents against individual streptococcal species

Antimicrobial agent	Inhibitory activity against indicated *Streptococcus* sp.[a]											
	S. mitis (n = 66)			*S. sanguinis* (n = 28)			*S. salivarius* (n = 12)			Nontypeable (n = 12)		
	MIC_{50}	MIC_{90}	No. (%) of NS[b] isolates	MIC_{50}	MIC_{90}	No. (%) of NS isolates	MIC_{50}	MIC_{90}	No. (%) of NS isolates	MIC_{50}	MIC_{90}	No. (%) of NS isolates
Penicillin	0.25	4	36 (55)	0.25	2	21 (75)	0.06	0.5	3 (25)	0.12	0.5	6 (50)
Ceftriaxone	0.25	2	18 (27)	0.06	1	4 (14)	≤0.03	0.25	1 (8)	≤0.03	0.5	1 (8)
Erythromycin	1	8	36 (55)	2	≥128	21 (75)	4	8	8 (67)	2	4	7 (58)
Clindamycin	≤0.25	4	7 (11)	≤0.25	≥128	5 (18)	≤0.25	8	2 (17)	≤0.25	0.25	1 (8)
TMP-SMX[c]	≤0.25	4	30 (45)	1	4	26 (93)	≤0.25	4	5 (42)	≤0.25	1	3 (25)
Ciprofloxacin	1	4	13 (20)[d]	1	4	3 (11)	1	2	0 (0)	1	2	0 (0)

[a] All MICs were measured in micrograms per milliliter.
[b] NS, nonsusceptible.
[c] TMP-SMX, trimethoprim-sulfamethoxazole at a 19:1 ratio.
[d] A breakpoint of ≥4 μg/ml was used.

isolates that were found to be resistant to ciprofloxacin, 13 (81%) were *S. mitis* isolates. These findings are in keeping with those of other investigators who have found higher rates of resistance in *S. mitis* than in other *Streptococcus* spp. (5, 19). VGS have emerged as significant pathogens in febrile neutropenic patients with cancer (1). The most frequently isolated VGS is *S. mitis* (1, 7, 16, 21). Risk factors for bacteremia with a resistant strain of VGS included previous therapy with a β-lactam and antimicrobial prophylaxis with a penicillin and/or a fluoroquinolone (1, 7, 9, 17). With the emergence of resistance in VGS isolated from blood, these factors should be taken into consideration when deciding on initial empirical therapy.

APPENDIX

The members of the Canadian Bacterial Surveillance Network and their participating laboratories were K. Green and S. Porter-Pong, Toronto Medical Laboratories and Mount Sinai Hospital, Toronto, Ontario; P. Kibsey, Victoria General Hospital, Victoria, British Columbia; R. Davidson and K. Forward, QEII Health Sciences Centre, Halifax, Nova Scotia; J. Blondeau, Royal University Hospital, Saskatoon, Saskatchewan; S. Hoban, St. Boniface General Hospital, Winnipeg, Manitoba; G. G. Zhanel, Health Sciences Centre, Winnipeg, Manitoba; M. Kuhn, Southeast Healthcare Corporation—Moncton Site, Moncton, New Brunswick; L. Thibault, Dr. Georges L. Dumont Hospital, Moncton, New Brunswick; M. J. Taylor, Westman Regional Laboratory, Brandon, Manitoba; N. Clerk, William Osler Health Center—Etobicoke, Toronto, Ontario; J. Downey, Toronto East General and Orthopedic Hospital Inc., Toronto, Ontario; M. Bergeron, Centre Hospitalier Universitaire de Québec, Université Laval, Sainte-Foy, Quebec; and G. S. Randhawa, Kelowna General Hospital, Kelowna, British Columbia.

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