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In Vitro Activity of Plazomicin against 5,015 Gram-Negative and Gram-Positive Clinical Isolates Obtained from Patients in Canadian Hospitals as Part of the CANWARD Study, 2011-2012

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Plazomicin is a next-generation aminoglycoside that is not affected by most clinically relevant aminoglycoside-modifying enzymes. The *in vitro* activities of plazomicin and comparator antimicrobials were evaluated against a collection of 5,015 bacterial isolates obtained from patients in Canadian hospitals between January 2011 and October 2012. Susceptibility testing was performed using the Clinical and Laboratory Standards Institute (CLSI) broth microdilution method, with MICs interpreted according to CLSI breakpoints, when available. Plazomicin demonstrated potent *in vitro* activity against members of the family *Enterobacteriaceae*, with all species except *Proteus mirabilis* having an MIC_{90} of ≤1 μg/ml. Plazomicin was active against aminoglycoside-nonsusceptible *Escherichia coli*, with MIC_{50} and MIC_{90} values identical to those for aminoglycoside-susceptible isolates. Furthermore, plazomicin demonstrated equivalent activities versus extended-spectrum β-lactamase (ESBL)-producing and non-ESBL-producing *E. coli* and *Klebsiella pneumoniae*, with 90% of the isolates inhibited by an MIC of ≤1 μg/ml. The MIC_{50} and MIC_{90} values for plazomicin against *Pseudomonas aeruginosa* were 4 μg/ml and 16 μg/ml, respectively, compared with 4 μg/ml and 8 μg/ml, respectively, for amikacin. Plazomicin had an MIC_{50} of 8 μg/ml and an MIC_{90} of 32 μg/ml versus 64 multidrug-resistant *P. aeruginosa* isolates. Plazomicin was active against methicillin-susceptible and methicillin-resistant *Staphylococcus aureus*, with both having MIC_{50} and MIC_{90} values of 0.5 μg/ml and 1 μg/ml, respectively. In summary, plazomicin demonstrated potent *in vitro* activity against a diverse collection of Gram-negative bacilli and Gram-positive cocci obtained over a large geographic area. These data support further evaluation of plazomicin in the clinical setting.

Multidrug-resistant (MDR) Gram-negative bacilli are being encountered in the clinical setting with increased frequency (1–4). Common examples include extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae*, carbapenemase-producing *Enterobacteriaceae*, and MDR *Pseudomonas aeruginosa*. These organisms are capable of causing serious infections, including bacteremia, pneumonia, and urinary tract infections (1–4). Furthermore, some publications have demonstrated an association between infection with MDR Gram-negative bacilli and adverse clinical outcomes, including increased mortality (5–9). The treatment of infections caused by these pathogens is challenging for clinicians, as often there are few viable therapeutic options. The Infectious Diseases Society of America (IDSA) recognizes the need for new antimicrobial agents with activity against Gram-negative bacilli (10). Their "10 × '20 Initiative" calls for the development and regulatory approval of 10 novel, efficacious, and safe antimicrobial agents by the year 2020 (10).

The aminoglycosides are among the oldest classes of antibiotics. They were originally introduced for therapeutic use in 1944 (11). Aminoglycosides demonstrate a broad spectrum of activity against bacteria, including members of the family *Enterobacteriaceae*, *P. aeruginosa*, and *Staphylococcus* spp. (11). However, the therapeutic use of aminoglycosides in recent years has been limited by concerns of toxicity (nephrotoxicity and ototoxicity) and increasing antimicrobial resistance (11). Resistance to aminoglycosides may be mediated by the production of aminoglycoside-modifying enzymes (AMEs), efflux, reduced permeability into the bacterial cell, and target site alteration by ribosomal methylases (11–13). Of these mechanisms, aminoglycoside-modifying enzymes provide the greatest contribution to resistance in clinical isolates (11, 14). The 3 major groups of AMEs are acetyltransferases, nucleotidyltransferases, and phosphotransferases (11). MDR Gram-negative bacilli are often resistant to aminoglycosides due to the effects of these enzymes (1, 15).

Plazomicin (formerly ACHN-490) is a next-generation aminoglycoside that was synthetically derived from sisomicin (13, 16). Unlike other aminoglycosides in clinical use, the *in vitro* activity of plazomicin does not appear to be compromised by most clinically relevant AMEs (13, 16, 17). This suggests that plazomicin may be of use in the treatment of infections caused by MDR Gram-negative bacilli. The purpose of this study was to evaluate the *in vitro* activity of plazomicin against a large collection of Gram-negative and Gram-positive clinical isolates obtained as a part of the Canadian Ward Surveillance study (CANWARD). CANWARD is an ongoing national surveillance study designed to assess the prevalence of antimicrobial resistance among bacterial isolates recovered from patients admitted to or evaluated at Canadian hospitals.

(This paper was presented in part at the 52nd Interscience Conference on Antimicrobial Agents and Chemotherapy [ICAAC], San Francisco, CA, 9 to 12 September 2012.)

Received 17 December 2013 **Returned for modification** 18 January 2014
Accepted 7 February 2014
Published ahead of print 18 February 2014
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doi:10.1128/AAC.02744-13

MATERIALS AND METHODS

Bacterial isolates. Twelve (2011) to 15 (2012) tertiary care medical centers representing 8 of the 10 Canadian provinces submitted pathogens from patients attending hospital clinics, emergency rooms, medical and surgical wards, and intensive care units (CANWARD). The sites were geographically distributed in a population-based fashion. From January 2011 through October 2012, inclusive, each study site was asked to submit clinical isolates (consecutive, one per patient per infection site) from inpatients and outpatients with bloodstream ($n = 100$), respiratory ($n = 100$), urine ($n = 25$), and wound/intravenous (i.v.) ($n = 25$) infections. The medical centers submitted clinically significant isolates, as defined by their local site criteria. Isolate identification was performed by the submitting site and confirmed at the reference site as required (i.e., when morphological characteristics and antimicrobial susceptibility patterns did not fit the reported identification). The isolates were shipped on Amies semisolid transport medium to the coordinating laboratory (Health Sciences Centre, Winnipeg, Manitoba, Canada), subcultured onto the appropriate medium, and stocked in skim milk at −80°C until MIC testing was carried out.

In total, 6,593 isolates were collected over the 2 years of the study. The demographic distribution of these isolates, by specimen source, was 43.5% from blood, 36.8% from respiratory, 10.2% from urine, 9.5% from wound, and by patient location was 28.8% from a medical ward, 23.9% from an emergency room, 22.7% from an intensive care unit, 17.1% from a hospital clinic, and 7.5% from a surgical ward. Only species for which ≥30 isolates were tested against plazomicin were included in the analysis (with the exception of ESBL-producing *Klebsiella pneumoniae*).

Antimicrobial susceptibility testing. Following two subcultures from frozen stock, the *in vitro* activities of plazomicin and clinically relevant comparator antimicrobials were determined by broth microdilution in accordance with the Clinical and Laboratory Standards Institute (CLSI) guidelines (18, 19). The antimicrobial agents used in this study were obtained as laboratory-grade powders from their respective manufacturers. Plazomicin was obtained from Achaogen (San Francisco, CA). Antimicrobial MIC interpretive standards were defined according to CLSI breakpoints (18). Tigecycline MICs were interpreted using Food and Drug Administration (FDA)-defined breakpoints. At present, no breakpoints have been set for plazomicin.

ESBL-producing *E. coli* and *K. pneumoniae*. Screening for ESBL production among *Escherichia coli* and *K. pneumoniae* clinical isolates was performed as described by CLSI (18). Phenotypic confirmatory testing was done by the disk diffusion method according to CLSI guidelines, using disks containing ceftazidime (30 μg), ceftazidime-clavulanate (30 μg and 10 μg), cefotaxime (30 μg), and cefotaxime-clavulanate (30 μg and 10 μg) (18).

Methicillin-resistant *S. aureus* confirmation. All methicillin-resistant *Staphylococcus aureus* (MRSA) isolates were phenotypically confirmed using the cefoxitin disk test, as described by CLSI in the document M100-S23 (18). PCR amplification of the *mecA* gene was also performed.

MDR *P. aeruginosa*. MDR *P. aeruginosa* isolates were defined as isolates demonstrating nonsusceptibility to at least one antimicrobial from three or more different classes. For the purpose of this report, the five antimicrobial classes considered were aminoglycosides (amikacin, gentamicin, and tobramycin), fluoroquinolones (ciprofloxacin), antipseudomonal cephalosporins (ceftazidime), antipseudomonal penicillins (piperacillin-tazobactam), and antipseudomonal carbapenems (meropenem).

RESULTS

Plazomicin was evaluated against 5,015 clinical isolates, including 2,773 Gram-negative bacilli and 2,242 Gram-positive cocci. The *in vitro* activities of plazomicin and comparator antimicrobials against commonly encountered Gram-negative bacilli are presented in Table 1. The MIC_{90} of plazomicin versus *E. coli* was 4 times lower than that of tobramycin and amikacin and 16 times lower than that of gentamicin. The *in vitro* activity of plazomicin versus *E. coli* did not differ for aminoglycoside-susceptible and aminoglycoside-nonsusceptible isolates. The plazomicin MIC_{50} and MIC_{90} values were 0.5 μg/ml and 1 μg/ml, respectively, for gentamicin-susceptible and gentamicin-nonsusceptible *E. coli* (Table 2). Identical MIC_{50} and MIC_{90} values were also obtained for plazomicin versus *E. coli* isolates that were susceptible and nonsusceptible to tobramycin (Table 2). Plazomicin was equally active against ESBL-producing and non-ESBL-producing *E. coli* and *K. pneumoniae* isolates (Table 3). More than 90% of the *E. coli* and *K. pneumoniae* isolates were inhibited *in vitro* by ≤1 μg/ml of plazomicin, irrespective of whether they produced an ESBL enzyme. Plazomicin demonstrated potent *in vitro* activity versus other members of the family *Enterobacteriaceae* (Table 1), with all species except *Proteus mirabilis* having an MIC_{90} value of ≤1 μg/ml. In general, the *in vitro* activity of plazomicin was comparable to that of conventional aminoglycosides versus *Enterobacteriaceae* other than *E. coli*. However, it should be noted that for most species evaluated here, relatively few isolates demonstrating resistance to conventional aminoglycosides were included.

The MIC_{90} value of plazomicin for *P. aeruginosa* was 2 times higher than that for amikacin and gentamicin and 8 times higher than that for tobramycin (Table 1). *P. aeruginosa* isolates that were nonsusceptible to amikacin, gentamicin, and tobramycin had plazomicin MIC_{50} values that were 2 times (for tobramycin) to 16 times (for amikacin) higher than for isolates susceptible to these antimicrobials (Table 2). Plazomicin had an MIC_{90} of 32 μg/ml versus MDR *P. aeruginosa*, which was identical to that for amikacin. Similar to other aminoglycosides, plazomicin demonstrated poor *in vitro* activity against *Stenotrophomonas maltophilia* isolates, with an MIC_{50} of 64 μg/ml.

The *in vitro* activities of plazomicin versus common Gram-positive cocci are presented in Table 4. Plazomicin demonstrated potent activity against both methicillin-susceptible *S. aureus* (MSSA) and MRSA, with >90% of isolates being inhibited by an MIC of ≤1 μg/ml. Plazomicin was also active versus *Staphylococcus epidermidis*, with an MIC_{90} of 0.5 μg/ml. The *in vitro* activity of plazomicin versus *Enterococcus faecalis*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and *Streptococcus agalactiae* was generally poor, with MIC_{50} values ranging from 16 to 64 μg/ml and MIC_{90} values ranging from 32 to >64 μg/ml. Plazomicin demonstrated some *in vitro* activity versus *Enterococcus faecium*, with MIC_{50} and MIC_{90} values of 8 μg/ml and 16 μg/ml, respectively.

DISCUSSION

In this study, the *in vitro* activity of plazomicin was evaluated against a collection of clinically significant Gram-negative bacilli and Gram-positive cocci obtained from patients assessed at hospitals in Canada. Plazomicin demonstrated potent *in vitro* activity versus members of the family *Enterobacteriaceae*, including aminoglycoside-nonsusceptible *E. coli* and ESBL-producing *E. coli* and *K. pneumoniae*. Similar results have been reported by other investigators (13, 16, 17, 20–24). Furthermore, many of these studies also specifically evaluated the activity of plazomicin against collections of antimicrobial-resistant isolates (20–22). Galani et al. (20) assessed the *in vitro* activity of plazomicin against 300 MDR *Enterobacteriaceae* from Athens, Greece. The isolates tested in this study included ESBL producers and carbapenemase (*K. pneumoniae* carbapenemase [KPC] and VIM) producers. For these isolates, plazomicin had an MIC_{50} of 1 μg/ml and an MIC_{90} of 2

TABLE 1 *In vitro* activities of plazomicin and comparators against Gram-negative organisms

Organism (*n*) and antibiotic	MIC (μg/ml)			% of isolates that are:		
	50%	90%	Range	Susceptible	Intermediate	Resistant
Escherichia coli (1,146)						
Plazomicin	0.5	1	≤0.12–4	ND[a]	ND	ND
Amikacin	2	4	≤1–32	99.7	0.3	0.0
Gentamicin	≤0.5	16	≤0.5 to >32	89.0	0.5	10.5
Tobramycin	≤0.5	4	≤0.5 to >64	90.4	4.8	4.8
Cefazolin	2	64	≤0.5 to >128	71.6	9.9	18.5
Ceftazidime	≤0.25	2	≤0.25 to >32	92.9	0.8	6.3
Ceftriaxone	≤0.25	0.5	≤0.25 to >64	90.7	0.3	9.0
Ciprofloxacin	≤0.06	>16	≤0.06 to >16	73.5	0.2	26.4
Ertapenem	≤0.03	0.06	≤0.03–8	99.8	0.0	0.2
Meropenem	≤0.03	≤0.03	≤0.03–1	100.0	0.0	0.0
Piperacillin-tazobactam	≤1	4	≤1 to >512	97.7	0.6	1.7
Tigecycline	0.25	0.5	0.12–2	100.0	0.0	0.0
Trimethoprim-sulfamethoxazole	≤0.12	>8	≤0.12 to >8	71.1	ND	28.3
Klebsiella pneumoniae (395)						
Plazomicin	0.25	0.5	≤0.12 to >64	ND	ND	ND
Amikacin	≤1	≤1	≤1 to >64	99.7	0.0	0.3
Gentamicin	≤0.5	≤0.5	≤0.5 to >32	98.2	0.0	1.8
Tobramycin	≤0.5	≤0.5	≤0.5 to >64	98.2	0.8	1.0
Cefazolin	1	4	≤0.5 to >128	88.6	3.8	7.6
Ceftazidime	≤0.25	0.5	≤0.25 to >32	96.5	0.0	3.5
Ceftriaxone	≤0.25	≤0.25	≤0.25 to >64	95.2	1.0	3.8
Ciprofloxacin	≤0.06	0.25	≤0.06 to >16	94.7	0.8	4.6
Ertapenem	≤0.03	0.06	≤0.03–16	99.0	0.8	0.3
Meropenem	≤0.03	0.06	≤0.03–8	99.7	0.0	0.3
Piperacillin-tazobactam	2	4	≤1 to >512	97.7	0.8	1.5
Tigecycline	0.5	1	0.06–8	96.4	3.0	0.5
Trimethoprim-sulfamethoxazole	≤0.12	2	≤0.12 to >8	91.6	ND	8.4
Enterobacter cloacae (173)						
Plazomicin	0.25	0.5	≤0.12–2	ND	ND	ND
Amikacin	≤1	2	≤1–16	100.0	0.0	0.0
Gentamicin	≤0.5	≤0.5	≤0.5 to >32	95.4	0.0	4.6
Tobramycin	≤0.5	1	≤0.5–64	95.4	2.9	1.7
Cefazolin	>128	>128	2 to >128	1.7	1.7	96.5
Ceftazidime	0.5	>32	≤0.25 to >32	72.3	0.6	27.2
Ceftriaxone	≤0.25	>64	≤0.25 to >64	69.4	1.7	28.9
Ciprofloxacin	≤0.06	0.25	≤0.06 to >16	93.1	1.7	5.2
Ertapenem	0.06	1	≤0.03–32	86.1	6.9	6.9
Meropenem	≤0.03	0.12	≤0.03–2	98.8	1.2	0.0
Piperacillin-tazobactam	2	128	≤1–256	82.1	6.9	11.0
Tigecycline	0.5	1	0.25–8	96.5	1.7	1.7
Trimethoprim-sulfamethoxazole	≤0.12	4	≤0.12 to >8	89.0	ND	11.0
Klebsiella oxytoca (113)						
Plazomicin	0.25	0.5	≤0.12–1	ND	ND	ND
Amikacin	≤1	2	≤1–4	100.0	0.0	0.0
Gentamicin	≤0.5	≤0.5	≤0.5–1	100.0	0.0	0.0
Tobramycin	≤0.5	≤0.5	≤0.5–2	100.0	0.0	0.0
Cefazolin	4	>128	1 to >128	29.2	28.3	42.5
Ceftazidime	≤0.25	0.5	≤0.25 to >32	99.1	0.0	0.9
Ceftriaxone	≤0.25	0.5	≤0.25–32	93.8	0.9	5.3
Ciprofloxacin	≤0.06	≤0.06	≤0.06 to >16	99.1	0.0	0.9
Ertapenem	≤0.03	≤0.03	≤0.03–0.12	100.0	0.0	0.0
Meropenem	≤0.03	≤0.03	≤0.03–0.06	100.0	0.0	0.0
Piperacillin-tazobactam	≤1	128	≤1 to >512	87.6	0.9	11.5
Tigecycline	0.5	1	0.12–1	100.0	0.0	0.0
Trimethoprim-sulfamethoxazole	≤0.12	≤0.12	≤0.12 to >8	98.2	ND	1.8

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TABLE 1 (Continued)

Organism (*n*) and antibiotic	MIC (μg/ml)			% of isolates that are:		
	50%	90%	Range	Susceptible	Intermediate	Resistant
Serratia marcescens (109)						
Plazomicin	0.5	1	≤0.12–4	ND	ND	ND
Amikacin	2	2	≤1–16	100.0	0.0	0.0
Gentamicin	≤0.5	1	≤0.5 to >32	99.1	0.0	0.9
Tobramycin	1	2	≤0.5–32	96.3	1.8	1.8
Cefazolin	>128	>128	2 to >128	0.9	0.0	99.1
Ceftazidime	≤0.25	1	≤0.25–2	100.0	0.0	0.0
Ceftriaxone	≤0.25	1	≤0.25–8	91.7	2.8	5.5
Ciprofloxacin	≤0.06	2	≤0.06 to >16	86.2	6.4	7.3
Ertapenem	≤0.03	0.12	≤0.03–1	99.1	0.9	0.0
Meropenem	0.06	0.06	≤0.03–0.12	100.0	0.0	0.0
Piperacillin-tazobactam	≤1	4	≤1–256	94.5	4.6	0.9
Tigecycline	1	2	1–8	95.4	3.7	0.9
Trimethoprim-sulfamethoxazole	0.5	1	≤0.12 to >8	95.4	ND	4.6
Proteus mirabilis (85)						
Plazomicin	2	4	0.25–8	ND	ND	ND
Amikacin	2	4	≤1–8	100.0	0.0	0.0
Gentamicin	≤0.5	1	≤0.5 to >32	91.8	1.2	7.1
Tobramycin	≤0.5	2	≤0.5–16	96.5	1.2	2.4
Cefazolin	4	8	2 to >128	1.2	72.9	25.9
Ceftazidime	≤0.25	≤0.25	≤0.25–4	100.0	0.0	0.0
Ceftriaxone	≤0.25	≤0.25	≤0.25–2	96.5	3.5	0.0
Ciprofloxacin	≤0.06	4	≤0.06 to >16	87.1	2.4	10.6
Ertapenem	≤0.03	≤0.03	≤0.03–0.06	100.0	0.0	0.0
Meropenem	0.06	0.12	≤0.03–0.25	100.0	0.0	0.0
Piperacillin-tazobactam	≤1	≤1	≤1 to ≤1	100.0	0.0	0.0
Tigecycline	4	8	1–8	21.2	55.3	23.5
Trimethoprim-sulfamethoxazole	≤0.12	>8	≤0.12 to >8	80.0	ND	20.0
Enterobacter aerogenes (55)						
Plazomicin	0.25	0.5	≤0.12–2	ND	ND	ND
Amikacin	≤1	2	≤1–4	100.0	0.0	0.0
Gentamicin	≤0.5	≤0.5	≤0.5–1	100.0	0.0	0.0
Tobramycin	≤0.5	1	≤0.5–8	96.4	3.6	0.0
Cefazolin	32	>128	1 to >128	14.5	5.5	80.0
Ceftazidime	≤0.25	32	≤0.25 to >32	78.2	5.5	16.4
Ceftriaxone	≤0.25	16	≤0.25 to >64	69.1	3.6	27.3
Ciprofloxacin	≤0.06	0.5	≤0.06–8	96.4	0.0	3.6
Ertapenem	0.12	0.5	≤0.03–8	90.9	5.5	3.6
Meropenem	0.06	0.12	≤0.03–0.5	100.0	0.0	0.0
Piperacillin-tazobactam	2	16	≤1–128	92.7	5.5	1.8
Tigecycline	1	1	0.25–4	96.3	3.7	0.0
Trimethoprim-sulfamethoxazole	≤0.12	0.5	≤0.12–8	98.1	ND	1.9
Pseudomonas aeruginosa (593)						
Plazomicin	4	16	≤0.12 to >64	ND	ND	ND
Amikacin	4	8	≤1 to >64	94.6	2.9	2.5
Gentamicin	1	8	≤0.5 to >32	89.2	4.4	6.4
Tobramycin	≤0.5	2	≤0.5 to >64	94.4	1.0	4.6
Ceftazidime	2	16	≤0.25 to >32	85.7	4.6	9.8
Ciprofloxacin	0.25	4	≤0.06 to >16	80.4	7.6	12.0
Meropenem	0.5	4	≤0.03 to >32	83.0	7.6	9.4
Piperacillin-tazobactam	4	32	≤1 to >512	85.8	8.3	5.9
MDR[b] *Pseudomonas aeruginosa* (64)						
Plazomicin	8	32	0.25 to >64	ND	ND	ND
Amikacin	4	32	≤1 to >64	76.6	14.1	9.4
Gentamicin	4	>32	≤0.5 to >32	53.1	9.4	37.5
Tobramycin	1	64	≤0.5 to >64	68.8	1.6	29.7

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TABLE 1 (Continued)

Organism (*n*) and antibiotic	MIC (μg/ml)			% of isolates that are:		
	50%	90%	Range	Susceptible	Intermediate	Resistant
Ceftazidime	32	>32	2 to >32	17.2	20.3	62.5
Ciprofloxacin	4	>16	0.25 to >16	20.3	28.1	51.6
Meropenem	4	32	0.12 to >32	28.1	23.4	48.4
Piperacillin-tazobactam	64	256	4 to >512	20.3	15.6	64.1
Stenotrophomonas maltophilia (104)						
Plazomicin	64	>64	2 to >64	ND	ND	ND
Amikacin	64	>64	4 to >64	ND	ND	ND
Gentamicin	16	>32	1 to >32	ND	ND	ND
Tobramycin	16	>64	1 to >64	ND	ND	ND
Ceftazidime	>32	>32	1 to >32	23.1	7.7	69.2
Ciprofloxacin	2	8	0.5 to >16	ND	ND	ND
Tigecycline	1	4	0.25–8	ND	ND	ND
Trimethoprim-sulfamethoxazole	0.5	>8	≤0.12 to >8	78.8	ND	21.2

[a] ND, breakpoints not defined.
[b] MDR is defined as isolates demonstrating nonsusceptibility to at least one antimicrobial from three of the following five antimicrobial classes: aminoglycosides (amikacin, gentamicin, and tobramycin), fluoroquinolones (ciprofloxacin), antipseudomonal cephalosporins (ceftazidime), antipseudomonal penicillins (piperacillin-tazobactam), and antipseudomonal carbapenems (meropenem).

μg/ml (20). Similarly, Endimiani et al. (21) evaluated the *in vitro* activity of plazomicin against 25 KPC-producing *K. pneumoniae* isolates. In this publication, plazomicin demonstrated an MIC_{50} of 0.5 μg/ml and an MIC_{90} of 1 μg/ml (21). The current study adds to the literature, as it describes the *in vitro* activity of plazomicin against a large collection of randomly selected clinical isolates obtained across a broad geographic area (the country of Canada).

Aminoglycoside resistance among *Enterobacteriaceae* is most commonly mediated by AMEs (11, 14). Aggen et al. (16) previously demonstrated that almost all common AMEs, with the exception of AAC(2′)-I, have no effect on the activity of plazomicin. Data published by Landman et al. (17) support this finding. Of concern, however, the *in vitro* activity of plazomicin does appear to be compromised by the presence of ribosomal methylases, including the ArmA methylase and RmtC methylase (16, 22). These enzymes have been described in MDR Gram-negative bacilli (22). Among 17 NDM carbapenemase-producing *Enterobacteriaceae* isolates evaluated by Livermore et al. (22), 16 had a plazomicin MIC of ≥64 μg/ml. Fifteen of these isolates were found to have genes encoding 16S rRNA methylases (22). Fortunately, this resistance mechanism appears to be relatively uncommon at present. In the current study, the retained *in vitro* activity of plazomicin against aminoglycoside-nonsusceptible *E. coli* indicates that aminoglycoside resistance among these isolates was most likely mediated by AMEs. Additionally, the lack of high plazomicin MICs versus *E. coli* and other *Enterobacteriaceae* supports the current rarity of 16S rRNA methylases as a cause of aminoglycoside resistance among *Enterobacteriaceae* in Canada.

In this study, plazomicin demonstrated potent *in vitro* activity versus *P. aeruginosa*. While gentamicin and tobramycin had MIC_{90} values that were 2 times and 8 times lower than that of plazomicin, respectively, the significance of this observation needs to be interpreted with caution. The anticipated dosing, maximum serum concentration achieved, and area under the concentration time curve (AUC) are much higher for plazomicin than for gentamicin and tobramycin, so directly comparing the MICs for these antimicrobials in terms of clinical relevance is difficult (13, 25). The *in vitro* activity of plazomicin versus *P.*

TABLE 2 *In vitro* activity of plazomicin against aminoglycoside-susceptible and nonsusceptible *E. coli* and *P. aeruginosa*

Organism and antibiotic (no. of isolates)[a]	No. (cumulative %) of isolates with an MIC of:									
	≤0.25	0.5	1	2	4	8	16	32	64	>64
Escherichia coli										
Gentamicin S (1,020)	198 (19.4)	578 (76.1)	218 (97.4)	21 (99.5)	5 (100.0)					
Gentamicin NS (126)	18 (14.3)	69 (69.0)	36 (97.6)	3 (100.0)						
Tobramycin S (1,036)	203 (19.6)	590 (76.5)	216 (97.4)	22 (99.5)	5 (100.0)					
Tobramycin NS (110)	13 (11.8)	57 (63.6)	38 (98.2)	2 (100.0)						
Pseudomonas aeruginosa										
Amikacin S (561)	15 (2.7)	8 (4.1)	37 (10.7)	155 (38.3)	184 (71.1)	109 (90.6)	46 (98.8)	7 (100.0)		
Amikacin NS (32)	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.3)	0 (6.3)	2 (12.5)	1 (15.6)	10 (46.9)	9 (75.0)	8 (100.0)
Gentamicin S (529)	14 (2.6)	8 (4.2)	37 (11.2)	156 (40.6)	179 (74.5)	101 (93.6)	32 (99.6)	2 (100.0)		
Gentamicin NS (64)	1 (1.6)	0 (1.6)	0 (1.6)	1 (3.1)	5 (10.9)	10 (26.6)	15 (50.0)	15 (73.4)	9 (87.5)	8 (100.0)
Tobramycin S (560)	14 (2.5)	8 (3.9)	37 (10.5)	154 (38.0)	179 (70.0)	102 (88.2)	42 (95.7)	16 (98.6)	8 (100.0)	
Tobramycin NS (33)	1 (3.0)	0 (3.0)	0 (3.0)	3 (12.1)	5 (27.3)	9 (54.5)	5 (69.7)	1 (72.7)	1 (75.8)	8 (100.0)

[a] S, susceptible; NS, nonsusceptible.

TABLE 3 *In vitro* activities of plazomicin and comparators against ESBL-producing and non-ESBL-producing *E. coli* and *K. pneumoniae* isolates

Organism (*n*) and antibiotic	MIC (μg/ml)			% of isolates that are:		
	50%	90%	Range	Susceptible	Intermediate	Resistant
ESBL-producing *E. coli* (84)						
Plazomicin	0.5	1	≤0.12–2	ND[a]	ND	ND
Amikacin	2	8	≤1–32	96.4	3.6	0.0
Gentamicin	1	>32	≤0.5 to >32	58.3	0.0	41.7
Tobramycin	8	32	≤0.5 to >64	46.4	10.7	42.9
Cefazolin	>128	>128	32 to >128	0.0	0.0	100.0
Ceftazidime	16	>32	1 to >32	29.8	6.0	64.3
Ceftriaxone	64	>64	4 to >64	0.0	0.0	100.0
Ciprofloxacin	>16	>16	≤0.06 to >16	7.1	1.2	91.7
Ertapenem	0.06	0.25	≤0.03–2	98.8	0.0	1.2
Meropenem	≤0.03	≤0.03	≤0.03–0.06	100.0	0.0	0.0
Piperacillin-tazobactam	4	16	≤1–256	94.0	3.6	2.4
Tigecycline	0.5	0.5	0.12–1	100.0	0.0	0.0
Trimethoprim-sulfamethoxazole	>8	>8	≤0.12 to >8	40.5	ND	59.5
Non-ESBL-producing *E. coli* (1,062)						
Plazomicin	0.5	1	≤0.12–4	ND	ND	ND
Amikacin	2	4	≤1–32	99.9	0.1	0.0
Gentamicin	≤0.5	2	≤0.5 to >32	91.4	0.6	8.0
Tobramycin	≤0.5	2	≤0.5 to >64	93.9	4.3	1.8
Cefazolin	2	8	≤0.5 to >128	77.3	10.7	12.0
Ceftazidime	≤0.25	0.5	≤0.25 to >32	98.0	0.4	1.6
Ceftriaxone	≤0.25	≤0.25	≤0.25–64	97.9	0.4	1.7
Ciprofloxacin	≤0.06	>16	≤0.06 to >16	78.7	0.1	21.2
Ertapenem	≤0.03	≤0.03	≤0.03–8	99.9	0.0	0.1
Meropenem	≤0.03	≤0.03	≤0.03–1	100.0	0.0	0.0
Piperacillin-tazobactam	≤1	4	≤1 to >512	98.0	0.4	1.6
Tigecycline	0.25	0.5	0.12–2	100.0	0.0	0.0
Trimethoprim-sulfamethoxazole	≤0.12	>8	≤0.12 to >8	74.1	ND	25.9
ESBL-producing *K. pneumoniae* (15)						
Plazomicin	0.25	1	≤0.12 to >64	ND	ND	ND
Amikacin	≤1	16	≤1 to >64	93.3	0.0	6.7
Gentamicin	≤0.5	>32	≤0.5 to >32	66.7	0.0	33.3
Tobramycin	≤0.5	16	≤0.5 to >64	60.0	20.0	20.0
Cefazolin	>128	>128	8 to >128	0.0	0.0	100.0
Ceftazidime	32	>32	0.25 to >32	33.3	0.0	66.7
Ceftriaxone	32	>64	≤0.25 to >64	6.7	13.3	80.0
Ciprofloxacin	0.5	>16	≤0.06 to >16	53.3	6.7	40.0
Ertapenem	0.06	0.5	≤0.03–0.5	100.0	0.0	0.0
Meropenem	≤0.03	0.06	≤0.03–0.12	100.0	0.0	0.0
Piperacillin-tazobactam	8	128	2–512	80.0	6.7	13.3
Tigecycline	1	2	0.5–2	100.0	0.0	0.0
Trimethoprim-sulfamethoxazole	>8	>8	0.25 to >8	13.3	ND	86.7
Non-ESBL-producing *K. pneumoniae* (380)						
Plazomicin	0.25	0.5	≤0.12–1	ND	ND	ND
Amikacin	≤1	≤1	≤1–4	100.0	0.0	0.0
Gentamicin	≤0.5	≤0.5	≤0.5–16	99.5	0.0	0.5
Tobramycin	≤0.5	≤0.5	≤0.5–16	99.7	0.0	0.3
Cefazolin	1	2	≤0.5 to >128	92.1	3.9	3.9
Ceftazidime	≤0.25	0.5	≤0.25 to >32	98.9	0.0	1.1
Ceftriaxone	≤0.25	≤0.25	≤0.25 to >64	98.7	0.5	0.8
Ciprofloxacin	≤0.06	0.25	≤0.06 to >16	96.3	0.5	3.2
Ertapenem	≤0.03	≤0.03	≤0.03–16	98.9	0.8	0.3
Meropenem	≤0.03	≤0.03	≤0.03–8	99.7	0.0	0.3
Piperacillin-tazobactam	2	4	≤1 to >512	98.4	0.5	1.1
Tigecycline	0.5	1	0.06–8	96.3	3.2	0.5
Trimethoprim-sulfamethoxazole	≤0.12	1	≤0.12 to >8	94.7	ND	5.3

[a] ND, breakpoints not defined.

TABLE 4 *In vitro* activities of plazomicin and comparators against Gram-positive organisms

Organism (*n*) and antibiotic	MIC (μg/ml)			% of isolates that are:		
	50%	90%	Range	Susceptible	Intermediate	Resistant
Methicillin-susceptible *Staphylococcus aureus* (1,221)						
Plazomicin	1	1	≤0.12–4	ND[a]	ND	ND
Amikacin	4	4	≤1 to >64	99.5	0.3	0.2
Gentamicin	≤0.5	≤0.5	≤0.5 to >32	98.2	0.2	1.6
Tobramycin	≤0.5	≤0.5	≤0.5 to >64	97.4	0.3	2.3
Clindamycin	≤0.12	≤0.12	≤0.12 to >8	95.2	0.2	4.7
Doxycycline	≤0.12	0.25	≤0.12–16	98.9	0.7	0.4
Linezolid	2	4	≤0.12–4	100.0	ND	0.0
Tigecycline	0.12	0.25	0.06–0.5	100.0	ND	0.0
Trimethoprim-sulfamethoxazole	≤0.12	≤0.12	≤0.12 to >8	99.5	ND	0.5
Vancomycin	1	1	≤0.12–2	100.0	0.0	0.0
Methicillin-resistant *S. aureus* (266)						
Plazomicin	1	1	0.25–64	ND	ND	ND
Amikacin	8	32	≤1 to >64	80.1	16.9	3.0
Gentamicin	≤0.5	≤0.5	≤0.5 to >32	98.1	0.4	1.5
Tobramycin	1	>64	≤0.5 to >64	56.0	0.4	43.6
Clindamycin	≤0.12	>8	≤0.12 to >8	64.4	0.0	35.6
Doxycycline	≤0.12	0.25	≤0.12–16	98.9	0.8	0.4
Linezolid	2	4	0.5–4	100.0	ND	0.0
Tigecycline	0.12	0.25	0.06–2	98.5	ND	1.5
Trimethoprim-sulfamethoxazole	≤0.12	≤0.12	≤0.12 to >8	97.0	ND	3.0
Vancomycin	1	1	0.5–2	100.0	0.0	0.0
Staphylococcus epidermidis (143)						
Plazomicin	≤0.12	0.5	≤0.12–4	ND	ND	ND
Amikacin	≤1	16	≤1 to >64	97.2	0.7	2.1
Gentamicin	1	>32	≤0.5 to >32	53.9	7.7	38.5
Tobramycin	2	64	≤0.5 to >64	55.9	11.9	32.2
Cefazolin	1	64	≤0.5 to >128	ND	ND	ND
Clindamycin	≤0.12	>8	≤0.12 to >8	55.9	1.4	42.7
Doxycycline	0.25	1	≤0.12–32	96.5	2.8	0.7
Linezolid	0.5	1	≤0.12–4	100.0	ND	0.0
Tigecycline	0.12	0.25	≤0.03–1	ND	ND	ND
Trimethoprim-sulfamethoxazole	1	8	≤0.12 to >8	54.6	ND	45.5
Vancomycin	1	2	0.5–2	100.0	0.0	0.0
Streptococcus pneumoniae (323)						
Plazomicin	32	32	≤0.12–64	ND	ND	ND
Ceftriaxone[b]	≤0.12	≤0.12	≤0.12–4	99.1	0.6	0.3
Clindamycin	≤0.12	16	≤0.12 to >64	89.2	0.3	10.5
Doxycycline	≤0.25	2	≤0.25–16	84.8	0.9	14.2
Meropenem	≤0.06	0.12	≤0.06–1	92.6	4.3	3.1
Penicillin[b,c]	≤0.03	0.25	≤0.03–8	84.6	11.2	4.2
Tigecycline	≤0.015	0.03	≤0.015–0.06	100.0	ND	ND
Trimethoprim-sulfamethoxazole	0.25	1	≤0.12 to >8	86.7	5.3	8.0
Vancomycin	0.25	0.25	≤0.12–1	100.0	ND	ND
Streptococcus agalactiae (93)						
Plazomicin	64	>64	16 to >64	ND	ND	ND
Ceftriaxone	≤0.12	≤0.12	≤0.12 to ≤0.12	100.0	ND	ND
Clindamycin	≤0.12	>64	≤0.12 to >64	80.6	0.0	19.4
Linezolid	1	2	0.25–2	100.0	0.0	0.0
Meropenem	≤0.06	≤0.06	≤0.06 to ≤0.06	100.0	ND	ND
Penicillin	0.06	0.06	≤0.03–0.12	100.0	ND	ND
Tigecycline	0.06	0.06	≤0.015–0.12	100.0	ND	ND
Vancomycin	0.5	0.5	0.25–0.5	100.0	ND	ND

(Continued on following page)

TABLE 4 (Continued)

Organism (*n*) and antibiotic	MIC (μg/ml)			% of isolates that are:		
	50%	90%	Range	Susceptible	Intermediate	Resistant
Streptococcus pyogenes (81)						
Plazomicin	16	32	4–64	ND	ND	ND
Ceftriaxone	≤0.12	≤0.12	≤0.12 to ≤0.12	100.0	ND	ND
Clindamycin	≤0.12	≤0.12	≤0.12 to >64	98.8	0.0	1.2
Linezolid	1	2	0.25–2	100.0	ND	ND
Meropenem	≤0.06	≤0.06	≤0.06–0.12	100.0	ND	ND
Penicillin[c]	≤0.03	≤0.03	≤0.03–0.06	100.0	ND	ND
Tigecycline	0.03	0.06	≤0.015–0.25	100.0	ND	ND
Vancomycin	0.5	0.5	0.25–1	100.0	ND	ND
Enterococcus faecalis (45)						
Plazomicin	64	>64	2 to >64	ND	ND	ND
Amikacin	>64	>64	8 to >64	ND	ND	ND
Gentamicin	16	>32	1 to >32	ND	ND	ND
Tobramycin	16	>64	4 to >64	ND	ND	ND
Amoxicillin-clavulanate	0.5	1	0.12–1	ND	ND	ND
Ciprofloxacin	1	>16	0.25 to >16	71.1	6.7	22.2
Doxycycline	8	16	≤0.12–32	35.6	46.7	17.8
Linezolid	2	2	1–2	100.0	0.0	0.0
Piperacillin-tazobactam	4	4	≤1–8	ND	ND	ND
Tigecycline	0.12	0.12	≤0.03–0.25	100.0	ND	ND
Vancomycin	1	2	1–2	100.0	0.0	0.0
Enterococcus faecium (70)						
Plazomicin	8	16	2 to >64	ND	ND	ND
Amikacin	32	>64	8 to >64	ND	ND	ND
Gentamicin	8	>32	1 to >32	ND	ND	ND
Tobramycin	>64	>64	16 to >64	ND	ND	ND
Amoxicillin-clavulanate	>32	>32	0.12 to >32	ND	ND	ND
Ciprofloxacin	>16	>16	0.25 to >16	7.1	0.0	92.9
Doxycycline	1	8	≤0.12–16	88.6	2.9	8.6
Linezolid	2	4	0.5–4	75.4	24.6	0.0
Piperacillin-tazobactam	>512	>512	4 to >512	ND	ND	ND
Tigecycline	0.12	0.12	≤0.03–0.25	ND	ND	ND
Vancomycin	1	>32	0.5 to >32	72.5	0.0	27.5

[a] ND, breakpoints not defined.
[b] CLSI nonmeningitis breakpoints were used for ceftriaxone, and oral penicillin breakpoints were used for penicillin.
[c] Only 286 *S. pneumoniae* isolates and 74 *S. pyogenes* isolates were tested versus penicillin.

aeruginosa was similar to that for amikacin, an aminoglycoside for which the AUC appears to be more comparable (13). The data presented here are in agreement with results published by Landman et al. (26). These investigators evaluated plazomicin in comparison with amikacin versus 679 *P. aeruginosa* isolates. The MIC_{50} and MIC_{90} values of plazomicin were 8 μg/ml and 32 μg/ml, respectively, and for amikacin, 8 μg/ml and 16 μg/ml, respectively (26). In the present study, the activity of plazomicin versus MDR *P. aeruginosa* was similar to that of amikacin. It is interesting to note that *P. aeruginosa* isolates that were nonsusceptible to comparator aminoglycosides demonstrated relatively elevated MICs to plazomicin. The mechanisms resulting in elevated MICs of plazomicin versus *P. aeruginosa* remain poorly defined at this time, but it is likely that reduced permeability and/or efflux are contributing factors.

The excellent *in vitro* activity of plazomicin versus Gram-negative bacilli, including *P. aeruginosa* and aminoglycoside-nonsusceptible *Enterobacteriaceae*, suggests that there may be a role for this antimicrobial in the treatment of infections caused by these pathogens. Results from a phase 2 clinical trial of plazomicin for the treatment of complicated urinary tract infections and pyelonephritis compared to levofloxacin treatment have been reported in abstract form (27). Microbiological eradication in the modified intent-to-treat population was 58.7% (37/63 [95% confidence interval {CI}, 45.6% to 71.0%]) for plazomicin, compared with 58.6% (17/29 [95% CI, 38.9% to 76.5%]) for levofloxacin (27). Further studies are required to better define the clinical utility and adverse effect profile of this novel antimicrobial.

The data presented here also demonstrate potent *in vitro* activity of plazomicin versus both MSSA and MRSA. These data are in agreement with *in vitro* testing by Tenover et al. (28), who documented a plazomicin MIC_{50} of 1 μg/ml and an MIC_{90} of 2 μg/ml versus a collection of 493 MRSA isolates. In general, plazomicin had high MICs for other Gram-positive cocci, although modest activity was observed versus *E. faecium*. The clinical significance of this finding is uncertain, as conventional aminoglycosides are only used to treat enterococci in combination with a cell wall active agent versus isolates that do not demonstrate high-level aminogly-

coside resistance. An MIC cutoff for high-level plazomicin resistance among enterococci has not yet been defined.

There are several important limitations to this study. The number of aminoglycoside-nonsusceptible isolates for many species was small, precluding a subset analysis versus plazomicin. The molecular mechanisms conferring aminoglycoside resistance among Gram-negative isolates were not investigated, which was related to limited resources. This is of particular relevance for *P. aeruginosa*, for which further work is required to better define the mechanisms leading to elevated plazomicin MICs. Finally, limited space on the antimicrobial susceptibility panels precluded testing of additional relevant comparators.

In summary, plazomicin demonstrated potent *in vitro* activity against Gram-negative bacilli and Gram-positive cocci when evaluated against a large collection of bacterial isolates obtained from patients seen at hospitals across Canada. Plazomicin was active against aminoglycoside-nonsusceptible *E. coli*, with MIC values comparable to those for susceptible isolates. Furthermore, plazomicin demonstrated equivalent activity against ESBL-producing and non-ESBL-producing *E. coli* and *K. pneumoniae*. Plazomicin had similar activity to amikacin versus MDR *P. aeruginosa*. Plazomicin was also active against both MRSA and MSSA. The *in vitro* activity of plazomicin supports further evaluation of this antimicrobial in the clinical setting. If effective and well tolerated in clinical trials, plazomicin has the potential to help reach the "10 × '20" goal set by IDSA.

ACKNOWLEDGMENTS

We thank Barbara Weshnoweski, Ravinder Vashisht, and Nancy Laing for their technical assistance.

The CANWARD data are also displayed at www.can-r.ca, the official website of the Canadian Antimicrobial Resistance Alliance (CARA).

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