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In Vitro Activity of Plazomicin against Gram-Negative and Gram-Positive Bacterial Pathogens Isolated from Patients in Canadian Hospitals from 2013 to 2017 as Part of the CANWARD Surveillance Study

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ABSTRACT The Clinical and Laboratory Standards Institute (CLSI) broth microdilution method was used to evaluate the *in vitro* activities of plazomicin and comparator antimicrobial agents against 7,712 Gram-negative and 4,481 Gram-positive bacterial pathogens obtained from 2013 to 2017 from patients in Canadian hospitals as part of the CANWARD Surveillance Study. Plazomicin demonstrated potent *in vitro* activity against *Enterobacteriaceae* ($MIC_{90} \leq 1$ μg/ml for all species tested except *Proteus mirabilis* and *Morganella morganii*), including aminoglycoside-nonsusceptible, extended-spectrum β-lactamase (ESBL)-positive, and multidrug-resistant (MDR) isolates. Plazomicin was equally active against methicillin-susceptible and methicillin-resistant isolates of *Staphylococcus aureus*.

KEYWORDS aminoglycosides, Gram-negative bacteria, Gram-positive bacteria, multidrug resistance, plazomicin

Plazomicin is a semisynthetic aminoglycoside derived from sisomicin (1). Structural modifications protect plazomicin from inactivation by aminoglycoside-modifying enzymes, with the exception of the AAC(2′)-I enzyme, the gene for which is found on the chromosome of *Providencia stuartii* (1–4). Plazomicin consistently retains *in vitro* activity against Gram-negative bacilli resistant to other antimicrobial classes, including isolates harboring extended-spectrum β-lactamase (ESBL) enzymes, carbapenemase enzymes, and acquired colistin resistance genes (e.g., *mcr-1*) (5–9). Similar to other aminoglycosides, plazomicin is not active against Gram-negative bacilli that possess acquired 16S rRNA methyltransferase genes, but at present these remain uncommon in many parts of the world (3, 4, 8, 10–14). Data from recent clinical trials support a role for plazomicin in the treatment of complicated urinary tract infections, and the United States Food and Drug Administration (FDA) has recently approved the use of plazomicin for this indication (15–17). Clinical trial data also suggest a possible role for plazomicin in the treatment of infections caused by carbapenem-resistant *Enterobacteriaceae* (CRE) (18). The purpose of this study was to better characterize the *in vitro* activity of plazomicin versus a large collection of Gram-negative and Gram-positive bacteria obtained from patients across Canada as part of the ongoing Canadian ward Surveillance Study (CANWARD).

From January 2013 through October 2017, sentinel hospitals across Canada were requested on an annual basis to submit quotas of clinically significant isolates (consecutive isolates, one per patient per infection site) from inpatients and outpatients with bloodstream ($n = 100$), respiratory ($n = 100$), urine ($n = 25$), and wound/intravenous ($n = 25$) infections (CANWARD). Isolate identification was performed by the submitting site and confirmed at the reference site as required (i.e., when morphological characteristics and

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antimicrobial susceptibility patterns did not fit the reported identification). Isolates were shipped on Amies semisolid transport medium to the coordinating laboratory (Health Sciences Centre, Winnipeg, Manitoba, Canada), subcultured onto appropriate media, and stocked in skim milk at −80°C until MIC testing was carried out.

Following two subcultures from the frozen stock, the *in vitro* activities of plazomicin and clinically relevant comparator antimicrobials were determined by Clinical and Laboratory Standards Institute (CLSI)-defined broth microdilution testing using in-house-prepared 96-well broth microdilution panels (19). Antimicrobial MIC interpretive standards were defined according to CLSI breakpoints (20). Tigecycline MICs for *Enterobacteriaceae* were interpreted using FDA-defined breakpoints (susceptible, ≤2 μg/ml; intermediate, 4 μg/ml; resistant, ≥8 μg/ml), as CLSI MIC breakpoints are not currently published for this agent. FDA MIC interpretive breakpoints were used for plazomicin tested against *Enterobacteriaceae* (susceptible, ≤2 μg/ml; intermediate, 4 μg/ml; resistant, ≥8 μg/ml).

Phenotypic screening and confirmation of ESBL-producing *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Proteus mirabilis* were performed as described by CLSI (20). Multidrug-resistant (MDR) *Enterobacteriaceae* and *Pseudomonas aeruginosa* were defined as isolates nonsusceptible to ≥1 agent in ≥3 relevant antimicrobial categories (21). All methicillin-resistant *Staphylococcus aureus* (MRSA) isolates were phenotypically confirmed using the cefoxitin disk test (20).

The *in vitro* activities of plazomicin and comparator antimicrobials against 7,712 clinical isolates of Gram-negative bacteria are summarized in Table 1. Over 99% of *E. coli*, *K. pneumoniae*, *K. oxytoca*, *Enterobacter cloacae*, and *Klebsiella aerogenes* isolates were susceptible to plazomicin, with the MIC_{90} for these species ranging from 0.5 to 1 μg/ml. Relative to other *Enterobacteriaceae*, the plazomicin MIC_{90} values for clinical isolates of *P. mirabilis* and *Morganella morganii* were higher (4 μg/ml for both of these species). The MIC_{90} of plazomicin versus *P. aeruginosa* isolates was 16 μg/ml, comparable to the MIC_{90} of amikacin. Gentamicin and tobramycin were both more active than plazomicin *in vitro* against *P. aeruginosa* isolates. Plazomicin was less active than amikacin, gentamicin, and tobramycin versus *Acinetobacter baumannii*. Plazomicin demonstrated poor *in vitro* activity versus *Stenotrophomonas maltophilia*, which is considered intrinsically resistant to all aminoglycosides.

The *in vitro* activity of plazomicin versus comparator aminoglycoside-nonsusceptible *E. coli*, *K. pneumoniae*, and *P. aeruginosa* isolates is presented in Table 2. Plazomicin demonstrated excellent activity versus gentamicin- and tobramycin-nonsusceptible *Enterobacteriaceae* isolates. However, MIC values for plazomicin versus aminoglycoside-nonsusceptible *P. aeruginosa* isolates were higher than those versus the aminoglycoside-susceptible subset. Plazomicin retained *in vitro* activity versus ESBL-producing *E. coli* and *K. pneumoniae* isolates (Table 3), with MIC_{90} values being identical to those for non-ESBL producers. Table 4 depicts the *in vitro* activity of plazomicin versus MDR isolates. Overall, 99.4% of MDR *E. coli* isolates and 97.3% of MDR *K. pneumoniae* isolates remained susceptible to plazomicin. The MIC_{90} value for plazomicin versus MDR *P. aeruginosa* isolates was 64 μg/ml.

The *in vitro* activity of plazomicin versus 4,481 Gram-positive bacterial isolates is presented in Table 5. Plazomicin had an MIC_{90} of 1 μg/ml for both methicillin-susceptible *S. aureus* (MSSA) and MRSA isolates. Plazomicin was active against methicillin-susceptible and methicillin-resistant *Staphylococcus epidermidis* isolates, with MIC_{90} values of 0.25 μg/ml and 0.5 μg/ml, respectively. Plazomicin retained *in vitro* activity versus gentamicin-nonsusceptible *S. aureus* and *S. epidermidis* isolates (Table 6). Similar to the other aminoglycosides, plazomicin demonstrated poor *in vitro* activity versus *Enterococcus faecalis*, with an MIC_{90} of >64 μg/ml (Table 5). Plazomicin was the most active aminoglycoside evaluated versus *Enterococcus faecium* isolates, but it still had a relatively high MIC_{90} of 16 μg/ml.

In this study, plazomicin demonstrated excellent *in vitro* activity versus members of the family *Enterobacteriaceae*, including ESBL-producing, aminoglycoside-nonsusceptible, and MDR subsets. Similar data have been previously reported (5, 6, 22). In a recent publication, Castanheira et al. evaluated the *in vitro* activity of plazomicin and comparators versus 4,362

TABLE 1 *In vitro* activities of plazomicin and comparator agents against clinical isolates of Gram-negative bacteria

Organism (no. of isolates) and agent	MIC (μg/ml)			% of isolates		
	50%	90%	Range	Susceptible	Intermediate	Resistant
Escherichia coli (3,094)						
Plazomicin	0.5	1	≤0.12 to >64	99.5	0.4	0.1
Amikacin	2	4	≤1 to >64	99.8	0.1	0.1
Gentamicin	≤0.5	2	≤0.5 to >32	90.9	0.3	8.8
Tobramycin	≤0.5	4	≤0.5 to >64	91.8	2.7	5.5
Cefazolin	2	>128	≤0.5 to >128	70.9	8.8	20.3
Ceftazidime	≤0.25	4	≤0.25 to >32	90.8	1.5	7.7
Ceftriaxone	≤0.25	32	≤0.25 to >64	87.4	0.4	12.2
Ciprofloxacin	≤0.06	>16	≤0.06 to >16	75.3	0.1	24.6
Ertapenem	≤0.03	≤0.03	≤0.03 to >32	99.7	0.1	0.2
Meropenem	≤0.03	≤0.03	≤0.03 to 32	99.9	0	0.1
Piperacillin-tazobactam	2	4	≤1 to >512	97.1	1.5	1.4
Tigecycline	0.25	0.5	≤0.03 to 4	99.9	0.1	0
Trimethoprim-sulfamethoxazole	≤0.12	>8	≤0.12 to >8	73.0	NA[a]	27.0
Klebsiella pneumoniae (1,039)						
Plazomicin	0.25	0.5	≤0.12 to >64	99.8	0.1	0.1
Amikacin	≤1	2	≤1 to >64	99.9	0	0.1
Gentamicin	≤0.5	≤0.5	≤0.5 to >32	95.8	0	4.2
Tobramycin	≤0.5	≤0.5	≤0.5 to >64	94.5	2.6	2.9
Cefazolin	1	16	≤0.5 to >128	82.3	5.3	12.4
Ceftazidime	≤0.25	1	≤0.25 to >32	93.1	0.6	6.3
Ceftriaxone	≤0.25	≤0.25	≤0.25 to >64	91.9	0.1	8.0
Ciprofloxacin	≤0.06	1	≤0.06 to >16	91.6	1.8	6.6
Ertapenem	≤0.03	0.06	≤0.03 to >32	98.6	0.3	1.1
Meropenem	≤0.03	0.06	≤0.03 to 16	99.4	0.2	0.4
Piperacillin-tazobactam	2	8	≤1 to >512	95.6	1.6	2.8
Tigecycline	0.5	1	0.12 to >16	96.2	3.2	0.6
Trimethoprim-sulfamethoxazole	≤0.12	>8	≤0.12 to >8	87.9	NA	12.1
Enterobacter cloacae (470)						
Plazomicin	0.25	0.5	≤0.12 to 2	100	0	0
Amikacin	≤1	2	≤1 to 16	100	0	0
Gentamicin	≤0.5	≤0.5	≤0.5 to >32	97.9	0	2.1
Tobramycin	≤0.5	≤0.5	≤0.5 to >64	96.6	1.1	2.3
Cefazolin	>128	>128	1 to >128	1.9	1.7	96.4
Ceftazidime	0.5	>32	≤0.25 to >32	76.0	0.8	23.2
Ceftriaxone	≤0.25	>64	≤0.25 to >64	72.8	2.1	25.1
Ciprofloxacin	≤0.06	0.12	≤0.06 to >16	94.3	1.7	4.0
Ertapenem	0.06	0.5	≤0.03 to >32	91.3	5.1	3.6
Meropenem	≤0.03	0.12	≤0.03 to >32	99.4	0.2	0.4
Piperacillin-tazobactam	2	64	≤1 to >512	85.5	8.3	6.2
Tigecycline	0.5	1	0.12 to 8	95.5	2.4	2.1
Trimethoprim-sulfamethoxazole	≤0.12	1	≤0.12 to >8	91.5	NA	8.5
Klebsiella oxytoca (279)						
Plazomicin	0.25	0.5	≤0.12 to 2	100	0	0
Amikacin	≤1	2	≤1 to 8	100	0	0
Gentamicin	≤0.5	≤0.5	≤0.5 to >32	98.6	0.3	1.1
Tobramycin	≤0.5	≤0.5	≤0.5 to 32	99.3	0.3	0.4
Cefazolin	8	>128	≤0.5 to >128	27.6	22.2	50.2
Ceftazidime	≤0.25	0.5	≤0.25 to >32	98.6	0.3	1.1
Ceftriaxone	≤0.25	1	≤0.25 to >64	90.0	2.1	7.9
Ciprofloxacin	≤0.06	≤0.06	≤0.06 to >16	98.9	0.4	0.7
Ertapenem	≤0.03	≤0.03	≤0.03 to 0.12	100	0	0
Meropenem	≤0.03	0.06	≤0.03 to 0.5	100	0	0
Piperacillin-tazobactam	2	32	≤1 to >512	89.6	1.4	9.0
Tigecycline	0.5	0.5	0.12 to 4	99.3	0.7	0
Trimethoprim-sulfamethoxazole	≤0.12	≤0.12	≤0.12 to >8	97.1	NA	2.9
Serratia marcescens (255)						
Plazomicin	0.5	1	≤0.12 to 8	97.6	2.0	0.4
Amikacin	2	4	≤1 to 16	100	0	0
Gentamicin	≤0.5	1	≤0.5 to 8	99.6	0.4	0
Tobramycin	1	4	≤0.5 to 64	95.7	2.3	2.0

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TABLE 1 (Continued)

Organism (no. of isolates) and agent	MIC (μg/ml)			% of isolates		
	50%	90%	Range	Susceptible	Intermediate	Resistant
Cefazolin	>128	>128	128 to >128	0	0	100
Ceftazidime	0.5	1	≤0.25 to >32	99.2	0.4	0.4
Ceftriaxone	≤0.25	1	≤0.25 to >64	93.7	2.0	4.3
Ciprofloxacin	≤0.06	1	≤0.06 to 16	94.1	1.6	4.3
Ertapenem	≤0.03	0.12	≤0.03 to 16	98.0	1.2	0.8
Meropenem	0.06	0.06	≤0.03 to 8	99.2	0.4	0.4
Piperacillin-tazobactam	2	4	≤1 to 256	97.6	1.6	0.8
Tigecycline	2	4	0.5 to 16	88.2	10.2	1.6
Trimethoprim-sulfamethoxazole	0.5	1	≤0.12 to >8	96.9	NA	3.1
Proteus mirabilis (235)						
Plazomicin	4	4	0.5 to 32	44.3	46.3	9.4
Amikacin	4	8	≤1 to 32	98.7	1.3	0
Gentamicin	≤0.5	2	≤0.5 to >32	94.5	0.8	4.7
Tobramycin	≤0.5	1	≤0.5 to >64	95.3	1.3	3.4
Cefazolin	4	8	2 to >128	5.1	71.9	23.0
Ceftazidime	≤0.25	≤0.25	≤0.25 to 16	98.3	1.3	0.4
Ceftriaxone	≤0.25	≤0.25	≤0.25 to >64	97.9	0.8	1.3
Ciprofloxacin	≤0.06	2	≤0.06 to >16	88.1	3.0	8.9
Ertapenem	≤0.03	≤0.03	≤0.03 to 1	99.6	0.4	0
Meropenem	0.06	0.12	≤0.03 to 1	100	0	0
Piperacillin-tazobactam	≤1	≤1	≤1 to 64	99.1	0.9	0
Tigecycline	4	8	0.5 to 16	13.6	55.3	31.1
Trimethoprim-sulfamethoxazole	≤0.12	>8	≤0.12 to >8	80.9	NA	19.1
Klebsiella aerogenes (97)						
Plazomicin	0.5	0.5	≤0.12 to 2	100	0	0
Amikacin	≤1	2	≤1 to 8	100	0	0
Gentamicin	≤0.5	≤0.5	≤0.5 to 2	100	0	0
Tobramycin	≤0.5	≤0.5	≤0.5 to 16	99.0	0	1.0
Cefazolin	128	>128	1 to >128	3.1	3.1	93.8
Ceftazidime	0.5	>32	≤0.25 to >32	73.2	3.1	23.7
Ceftriaxone	≤0.25	32	≤0.25 to >64	72.2	0	27.8
Ciprofloxacin	≤0.06	0.12	≤0.06 to 8	96.9	1.0	2.1
Ertapenem	0.12	0.5	≤0.03 to >32	93.8	3.1	3.1
Meropenem	0.06	0.06	≤0.03 to 32	99.0	0	1.0
Piperacillin-tazobactam	4	32	≤1 to 256	83.5	14.4	2.1
Tigecycline	0.5	1	0.06 to 4	99.0	1.0	0
Trimethoprim-sulfamethoxazole	≤0.12	0.5	≤0.12 to >8	95.9	NA	4.1
Morganella morganii (54)						
Plazomicin	2	4	0.25 to 8	66.7	27.7	5.6
Amikacin	2	4	≤1 to 8	100	0	0
Gentamicin	≤0.5	32	≤0.5 to >32	88.9	0	11.1
Tobramycin	≤0.5	4	≤0.5 to 64	96.3	1.8	1.9
Cefazolin	>128	>128	8 to >128	0	0	100
Ceftazidime	≤0.25	16	≤0.25 to >32	83.3	5.6	11.1
Ceftriaxone	≤0.25	2	≤0.25 to >64	87.0	7.4	5.6
Ciprofloxacin	≤0.06	>16	≤0.06 to >16	83.3	0	16.7
Ertapenem	≤0.03	0.06	≤0.03 to 0.5	100	0	0
Meropenem	0.06	0.12	≤0.03 to 0.5	100	0	0
Piperacillin-tazobactam	≤1	2	≤1 to 256	98.1	0	1.9
Tigecycline	2	4	0.12 to 16	81.5	14.8	3.7
Trimethoprim-sulfamethoxazole	0.25	>8	≤0.12 to >8	83.3	NA	16.7
Pseudomonas aeruginosa (1,789)						
Plazomicin	4	16	≤0.12 to >64	NA	NA	NA
Amikacin	4	16	≤1 to >64	94.4	2.2	3.4
Gentamicin	1	8	≤0.5 to >32	89.5	4.4	6.1
Tobramycin	≤0.5	2	≤0.5 to >64	94.2	1.3	4.5
Ceftazidime	4	32	≤0.25 to >32	80.2	7.6	12.2
Ciprofloxacin	0.25	4	≤0.06 to >16	80.3	7.1	12.6
Meropenem	0.5	8	≤0.03 to >32	79.7	6.7	13.6
Piperacillin-tazobactam	4	64	≤1 to >512	83.0	8.7	8.3

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TABLE 1 (Continued)

Organism (no. of isolates) and agent	MIC (μg/ml)			% of isolates		
	50%	90%	Range	Susceptible	Intermediate	Resistant
Acinetobacter baumannii (68)						
Plazomicin	1	8	0.25 to >64	NA	NA	NA
Amikacin	≤1	4	≤1 to >64	98.5	0	1.5
Gentamicin	≤0.5	2	≤0.5 to >32	92.6	1.5	5.9
Tobramycin	≤0.5	1	≤0.5 to >64	97.1	1.4	1.5
Ceftazidime	8	16	1 to >32	77.9	17.7	4.4
Ceftriaxone	16	32	1 to >64	44.1	33.8	22.1
Ciprofloxacin	0.25	0.5	≤0.06 to >16	97.1	0	2.9
Meropenem	0.5	2	0.06 to >32	98.5	0	1.5
Piperacillin-tazobactam	4	32	≤1 to >512	83.8	13.3	2.9
Tigecycline	0.25	2	0.12 to 16	NA	NA	NA
Trimethoprim-sulfamethoxazole	≤0.12	0.5	≤0.12 to >8	94.1	NA	5.9
Stenotrophomonas maltophilia (332)						
Plazomicin	>64	>64	≤0.12 to >64	NA	NA	NA
Amikacin	>64	>64	≤1 to >64	NA	NA	NA
Gentamicin	32	>32	≤0.5 to >32	NA	NA	NA
Tobramycin	32	>64	≤0.5 to >64	NA	NA	NA
Ceftazidime	>32	>32	0.5 to >32	22.3	6.9	70.8
Ciprofloxacin	4	16	0.12 to >16	NA	NA	NA
Tigecycline	1	4	0.12 to 16	NA	NA	NA
Trimethoprim-sulfamethoxazole	0.25	1	≤0.12 to >8	97.3	NA	2.7

[a]NA, MIC breakpoint not applicable.

Enterobacteriaceae clinical isolates collected in the United States between 2014 and 2015 (22). The MIC_{90} values of plazomicin versus *E. coli* and *K. pneumoniae* were 1 μg/ml and 0.5 μg/ml, respectively, in line with what has been reported here (22). The MIC_{90} for plazomicin was 2 μg/ml versus gentamicin-resistant and tobramycin-resistant members of the family *Enterobacteriaceae* (22). The retained *in vitro* activity of plazomicin versus aminoglycoside-nonsusceptible *Enterobacteriaceae* presumably reflects the stability of this antimicrobial to common aminoglycoside-modifying enzymes (22). Lopez-Diaz et al. re-

TABLE 2 MIC distributions for plazomicin against aminoglycoside-susceptible and aminoglycoside-nonsusceptible *Enterobacteriaceae* and *Pseudomonas aeruginosa*

Organism (no. of isolates) and agent[a]	No. of isolates (cumulative percentage of isolates) with the following plazomicin MIC (μg/ml):										
	≤0.12	0.25	0.5	1	2	4	8	16	32	64	>64
Escherichia coli											
Amikacin S (3,087)	21 (0.7)	642 (21.5)	1,731 (77.6)	599 (97.0)	78 (99.5)	16 (100)					
Amikacin NS (7)			1 (14.3)	2 (42.9)	3 (85.7)						1 (100)
Gentamicin S (2,811)	21 (0.7)	596 (21.9)	1,565 (77.6)	540 (96.8)	75 (99.5)	14 (100)					
Gentamicin NS (283)		46 (16.3)	167 (75.3)	61 (96.8)	6 (98.9)	2 (99.6)					1 (100)
Tobramycin S (2,839)	21 (0.7)	621 (22.6)	1,579 (78.2)	529 (96.9)	75 (99.5)	14 (100)					
Tobramycin NS (255)		21 (8.2)	153 (68.2)	72 (96.5)	6 (98.8)	2 (99.6)					1 (100)
Klebsiella pneumoniae											
Amikacin S (1,038)	59 (5.7)	807 (83.4)	156 (98.5)	13 (99.7)	2 (99.9)	1 (100)					
Amikacin NS (1)											1 (100)
Gentamicin S (995)	58 (5.8)	777 (83.9)	147 (98.7)	11 (99.8)	1 (99.9)	1 (100)					
Gentamicin NS (44)	1 (2.3)	30 (70.5)	9 (90.9)	2 (95.5)	1 (97.7)						1 (100)
Tobramycin S (982)	56 (5.7)	766 (83.7)	146 (98.6)	11 (99.7)	2 (99.9)	1 (100)					
Tobramycin NS (57)	3 (5.3)	41 (77.2)	10 (94.7)	2 (98.2)							1 (100)
Pseudomonas aeruginosa											
Amikacin S (1,688)	7 (0.4)	27 (2.0)	42 (4.5)	83 (9.4)	481 (37.9)	556 (70.9)	299 (88.6)	157 (97.9)	34 (99.9)		2 (100)
Amikacin NS (101)						1 (1.0)	2 (3.0)	13 (15.8)	25 (40.6)	18 (58.4)	42 (100)
Gentamicin S (1,602)	7 (0.4)	24 (1.9)	40 (4.4)	83 (9.6)	476 (39.3)	544 (73.3)	280 (90.8)	138 (99.4)	10 (100)		
Gentamicin NS (187)		3 (1.6)	2 (2.7)		5 (5.3)	13 (12.3)	21 (23.5)	32 (40.6)	49 (66.8)	18 (76.5)	44 (100)
Tobramycin S (1,686)	7 (0.4)	25 (1.9)	41 (4.3)	82 (9.2)	476 (37.4)	543 (69.6)	280 (86.2)	160 (95.7)	55 (99.0)	12 (99.7)	5 (100)
Tobramycin NS (103)		2 (1.9)	1 (2.9)	1 (3.9)	5 (8.7)	14 (22.3)	21 (42.7)	10 (52.4)	4 (56.3)	6 (62.1)	39 (100)

[a]S, aminoglycoside susceptible; NS, aminoglycoside nonsusceptible.

TABLE 3 *In vitro* activities of plazomicin and comparators against ESBL-producing and non-ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* isolates

Organism (no. of isolates) and agent	MIC (μg/ml)			% of isolates		
	50%	90%	Range	Susceptible	Intermediate	Resistant
ESBL-producing *Escherichia coli* (343)						
Plazomicin	0.5	1	0.25 to 2	100	0	0
Amikacin	2	8	≤1 to 64	98.8	0.9	0.3
Gentamicin	≤0.5	>32	≤0.5 to >32	67.1	1.7	31.2
Tobramycin	4	32	≤0.5 to >64	55.7	7.0	37.3
Cefazolin	>128	>128	4 to >128	0	0.3	99.7
Ceftazidime	16	>32	0.5 to >32	31.8	11.6	56.6
Ceftriaxone	>64	>64	≤0.25 to >64	2.6	1.5	95.9
Ciprofloxacin	>16	>16	≤0.06 to >16	12.5	0	87.5
Ertapenem	≤0.03	0.12	≤0.03 to >32	98.0	0.8	1.2
Meropenem	≤0.03	0.06	≤0.03 to 32	99.7	0	0.3
Piperacillin-tazobactam	4	16	≤1 to >512	92.7	3.8	3.5
Tigecycline	0.25	1	0.12 to 2	100	0	0
Trimethoprim-sulfamethoxazole	>8	>8	≤0.12 to >8	32.4	NA[a]	67.6
Non-ESBL-producing *Escherichia coli* (2,751)						
Plazomicin	0.5	1	≤0.12 to >64	99.4	0.5	0.1
Amikacin	2	4	≤1 to >64	99.8	0.1	0.1
Gentamicin	≤0.5	1	≤0.5 to >32	93.8	0.2	6.0
Tobramycin	≤0.5	1	≤0.5 to >64	96.3	2.1	1.6
Cefazolin	2	8	≤0.5 to >128	79.7	9.9	10.4
Ceftazidime	≤0.25	0.5	≤0.25 to >32	98.1	0.3	1.6
Ceftriaxone	≤0.25	≤0.25	≤0.25 to >64	98.0	0.2	1.8
Ciprofloxacin	≤0.06	>16	≤0.06 to >16	83.1	0.1	16.8
Ertapenem	≤0.03	≤0.03	≤0.03 to 2	99.8	0.1	0.1
Meropenem	≤0.03	≤0.03	≤0.03 to 0.25	100	0	0
Piperacillin-tazobactam	2	4	≤1 to >512	97.6	1.3	1.1
Tigecycline	0.25	0.5	≤0.03 to 4	99.9	0.1	0
Trimethoprim-sulfamethoxazole	≤0.12	>8	≤0.12 to >8	78.1	NA	21.9
ESBL-producing *Klebsiella pneumoniae* (73)						
Plazomicin	0.25	0.5	≤0.12 to 4	98.6	1.4	0
Amikacin	2	8	≤1 to 16	100	0	0
Gentamicin	16	>32	≤0.5 to >32	49.3	0	50.7
Tobramycin	8	32	≤0.5 to >64	37.0	24.6	38.4
Cefazolin	>128	>128	8 to >128	0	0	100
Ceftazidime	>32	>32	0.5 to >32	17.8	5.5	76.7
Ceftriaxone	>64	>64	≤0.25 to >64	4.1	0	95.9
Ciprofloxacin	8	>16	≤0.06 to >16	23.3	10.9	65.8
Ertapenem	0.12	8	≤0.03 to >32	82.2	5.5	12.3
Meropenem	≤0.03	0.5	≤0.03 to 16	93.2	2.7	4.1
Piperacillin-tazobactam	16	>512	2 to >512	61.6	15.1	23.3
Tigecycline	1	2	0.5 to 4	91.8	8.2	0
Trimethoprim-sulfamethoxazole	>8	>8	≤0.12 to >8	6.8	NA	93.2
Non-ESBL-producing *Klebsiella pneumoniae* (966)						
Plazomicin	0.25	0.5	≤0.12 to >64	99.9	0	0.1
Amikacin	≤1	2	≤1 to >64	99.9	0	0.1
Gentamicin	≤0.5	≤0.5	≤0.5 to >32	99.3	0	0.7
Tobramycin	≤0.5	≤0.5	≤0.5 to >64	98.9	0.9	0.2
Cefazolin	1	4	≤0.5 to >128	88.5	5.7	5.8
Ceftazidime	≤0.25	0.5	≤0.25 to >32	98.8	0.3	0.9
Ceftriaxone	≤0.25	≤0.25	≤0.25 to >64	98.6	0.1	1.3
Ciprofloxacin	≤0.06	0.25	≤0.06 to >16	96.8	1.0	2.2
Ertapenem	≤0.03	≤0.03	≤0.03 to 32	99.8	0	0.2
Meropenem	≤0.03	0.06	≤0.03 to 8	99.9	0	0.1
Piperacillin-tazobactam	2	8	≤1 to >512	98.1	0.7	1.2
Tigecycline	0.5	1	0.12 to >16	96.5	2.9	0.6
Trimethoprim-sulfamethoxazole	≤0.12	0.5	≤0.12 to >8	94.0	NA	6.0

[a]NA, MIC breakpoint not applicable.

TABLE 4 *In vitro* activities of plazomicin and comparators against MDR *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*

Organism (no. of isolates) and agent	MIC (μg/ml)			% of isolates		
	50%	90%	Range	Susceptible	Intermediate	Resistant
MDR *Escherichia coli* (358)[a]						
Plazomicin	0.5	1	≤0.12 to >64	99.4	0.3	0.3
Amikacin	4	8	≤1 to >64	98.0	1.2	0.8
Gentamicin	1	>32	≤0.5 to >32	52.8	2.2	45.0
Tobramycin	8	32	≤0.5 to >64	42.5	14.2	43.3
Cefazolin	>128	>128	≤0.5 to >128	6.4	7.0	86.6
Ceftazidime	8	>32	≤0.25 to >32	46.1	8.4	45.5
Ceftriaxone	64	>64	≤0.25 to >64	22.1	1.1	76.8
Ciprofloxacin	>16	>16	≤0.06 to >16	4.2	0	95.8
Ertapenem	≤0.03	0.12	≤0.03 to >32	97.2	1.4	1.4
Meropenem	≤0.03	0.06	≤0.03 to 32	99.7	0	0.3
Piperacillin-tazobactam	4	64	≤1 to >512	86.3	5.9	7.8
Tigecycline	0.25	1	0.12 to 4	99.7	0.3	0
Trimethoprim-sulfamethoxazole	>8	>8	≤0.12 to >8	14.2	NA[c]	85.8
MDR *Klebsiella pneumoniae* (74)[a]						
Plazomicin	0.25	0.5	≤0.12 to >64	97.3	1.3	1.4
Amikacin	2	8	≤1 to >64	98.6	0	1.4
Gentamicin	32	>32	≤0.5 to >32	45.9	0	54.1
Tobramycin	8	32	≤0.5 to >64	31.1	28.4	40.5
Cefazolin	>128	>128	2 to >128	2.7	2.7	94.6
Ceftazidime	32	>32	≤0.25 to >32	24.3	6.8	68.9
Ceftriaxone	>64	>64	≤0.25 to >64	6.8	0	93.2
Ciprofloxacin	16	>16	≤0.06 to >16	14.9	9.4	75.7
Ertapenem	0.12	8	≤0.03 to >32	81.1	5.4	13.5
Meropenem	≤0.03	1	≤0.03 to 16	91.9	2.7	5.4
Piperacillin-tazobactam	16	>512	2 to >512	63.5	13.5	23.0
Tigecycline	1	4	0.5 to 4	87.8	12.2	0
Trimethoprim-sulfamethoxazole	>8	>8	0.25 to >8	2.7	NA	97.3
MDR *Pseudomonas aeruginosa* (256)[b]						
Plazomicin	8	64	≤0.12 to >64	NA	NA	NA
Amikacin	8	64	≤1 to >64	80.5	6.2	13.3
Gentamicin	4	>32	≤0.5 to >32	61.7	9.4	28.9
Tobramycin	1	64	≤0.5 to >64	72.3	4.7	23.0
Ceftazidime	32	>32	2 to >32	16.8	24.2	59.0
Ciprofloxacin	2	>16	≤0.06 to >16	30.9	21.4	47.7
Meropenem	8	32	0.25 to >32	15.2	21.5	63.3
Piperacillin-tazobactam	64	512	≤1 to >512	20.7	36.3	43.0

[a]MDR *Enterobacteriaceae* were defined as isolates nonsusceptible to ≥1 antimicrobial agent in ≥3 of the following antimicrobial agent categories: aminoglycosides (amikacin, gentamicin, tobramycin), antipseudomonal penicillins and β-lactamase inhibitors (piperacillin-tazobactam), carbapenems (ertapenem, meropenem), extended-spectrum cephalosporins (ceftazidime, ceftriaxone), fluoroquinolones (ciprofloxacin), folate pathway inhibitors (trimethoprim-sulfamethoxazole), and glycylcyclines (tigecycline).

[b]MDR *Pseudomonas aeruginosa* isolates were defined as isolates nonsusceptible to ≥1 antimicrobial agent in ≥3 of the following antimicrobial agent categories: aminoglycosides (amikacin, gentamicin, tobramycin), antipseudomonal penicillins and β-lactamase inhibitors (piperacillin-tazobactam), antipseudomonal carbapenems (meropenem), antipseudomonal cephalosporins (ceftazidime), and fluoroquinolones (ciprofloxacin).

[c]NA, MIC breakpoint not applicable.

cently assessed the *in vitro* activity of plazomicin versus 346 ESBL/AmpC-producing *E. coli* urinary isolates (6). Plazomicin had an MIC_{90} of 1 μg/ml, again, similar to the data that we have presented (6). The MIC values of plazomicin versus *P. aeruginosa* tend to be higher than those versus *Enterobacteriaceae*. In our study, the MIC_{50} and MIC_{90} values for *P. aeruginosa* were 4 μg/ml and 16 μg/ml, respectively. These data are consistent with what has been described elsewhere in the literature (22, 23).

In the present study, plazomicin demonstrated excellent *in vitro* activity versus *S. aureus* (both MRSA and MSSA) and coagulase-negative staphylococci. Similar *in vitro* activity versus MRSA has been described by Tenover et al. (24). These investigators assessed the *in vitro* activity of plazomicin versus 493 MRSA isolates from the United States. The MIC_{50} and MIC_{90} values for plazomicin were 1 μg/ml and 2 μg/ml, respectively (24). It should be noted that aminoglycosides are not typically used as mono-

TABLE 5 *In vitro* activities of plazomicin and comparator agents against clinical isolates of Gram-positive bacteria

Organism (no. of isolates) and agent	MIC (μg/ml)			% of isolates		
	50%	90%	Range	Susceptible	Intermediate	Resistant
Methicillin-susceptible *Staphylococcus aureus* (3,009)						
Plazomicin	0.5	1	≤0.12 to 16	NA[a]	NA	NA
Amikacin	2	4	≤1 to >64	NA	NA	NA
Gentamicin	≤0.5	≤0.5	≤0.5 to >32	98.6	0.1	1.3
Tobramycin	≤0.5	≤0.5	≤0.5 to >64	NA	NA	NA
Clindamycin	≤0.12	≤0.12	≤0.12 to >8	94.8	0.4	4.8
Doxycycline	≤0.12	0.25	≤0.12 to 32	98.8	0.9	0.3
Linezolid	2	4	≤0.12 to 4	100	NA	0
Tigecycline	0.12	0.25	≤0.03 to 2	99.7	NA	NA
Trimethoprim-sulfamethoxazole	≤0.12	≤0.12	≤0.12 to >8	99.7	NA	0.3
Vancomycin	0.5	1	≤0.12 to 2	100	0	0
Methicillin-resistant *Staphylococcus aureus* (687)						
Plazomicin	0.5	1	≤0.12 to 4	NA	NA	NA
Amikacin	8	32	≤1 to >64	NA	NA	NA
Gentamicin	≤0.5	≤0.5	≤0.5 to >32	96.2	0.6	3.2
Tobramycin	≤0.5	>64	≤0.5 to >64	NA	NA	NA
Clindamycin	≤0.12	>8	≤0.12 to >8	65.2	0	34.8
Doxycycline	≤0.12	1	≤0.12 to 16	97.2	1.2	1.6
Linezolid	2	4	0.5 to 4	100	NA	0
Tigecycline	0.25	0.25	≤0.03 to 1	98.3	NA	NA
Trimethoprim-sulfamethoxazole	≤0.12	≤0.12	≤0.12 to >8	98.0	NA	2.0
Vancomycin	0.5	1	≤0.12 to 4	99.7	0.3	0
Methicillin-susceptible *Staphylococcus epidermidis* (339)						
Plazomicin	≤0.12	0.25	≤0.12 to 2	NA	NA	NA
Amikacin	≤1	4	≤1 to 64	NA	NA	NA
Gentamicin	≤0.5	32	≤0.5 to >32	69.3	7.4	23.3
Tobramycin	≤0.5	16	≤0.5 to >64	NA	NA	NA
Clindamycin	≤0.12	>8	≤0.12 to >8	68.4	2.4	29.2
Doxycycline	0.25	1	≤0.12 to 32	96.2	1.2	2.6
Linezolid	1	2	≤0.12 to 2	100	NA	0
Tigecycline	0.12	0.25	≤0.03 to 1	NA	NA	NA
Trimethoprim-sulfamethoxazole	≤0.12	8	≤0.12 to >8	69.3	NA	30.7
Vancomycin	1	2	≤0.12 to 2	100	0	0
Methicillin-resistant *Staphylococcus epidermidis* (25)						
Plazomicin	0.25	0.5	≤0.12 to 0.5	NA	NA	NA
Amikacin	8	16	≤1 to 32	NA	NA	NA
Gentamicin	>32	>32	≤0.5 to >32	20.0	0	80.0
Tobramycin	32	>64	≤0.5 to >64	NA	NA	NA
Clindamycin	>8	>8	≤0.12 to >8	20.0	4.0	76.0
Doxycycline	0.5	1	≤0.12 to 2	100	0	0
Linezolid	1	1	0.5 to 2	100	NA	0
Tigecycline	0.25	0.25	0.06 to 0.5	NA	NA	NA
Trimethoprim-sulfamethoxazole	4	8	≤0.12 to 8	12.0	NA	88.0
Vancomycin	1	2	1 to 2	100	0	0
Enterococcus faecalis (301)						
Plazomicin	64	>64	1 to >64	NA	NA	NA
Amikacin	>64	>64	4 to >64	NA	NA	NA
Gentamicin	8	>32	≤0.5 to >32	NA	NA	NA
Tobramycin	16	>64	≤0.5 to >64	NA	NA	NA
Ciprofloxacin	1	>16	≤0.06 to >16	75.0	7.9	17.1
Doxycycline	8	16	≤0.12 to 32	37.1	44.8	18.1
Linezolid	2	4	0.5 to 4	3.3	16.7	0
Tigecycline	0.12	0.25	≤0.03 to 1	99.8	NA	NA
Vancomycin	1	2	0.5 to 4	100	0	0
Enterococcus faecium (120)						
Plazomicin	4	16	1 to 16	NA	NA	NA
Amikacin	32	>64	8 to >64	NA	NA	NA
Gentamicin	4	>32	≤0.5 to >32	NA	NA	NA
Tobramycin	64	>64	4 to >64	NA	NA	NA
Ciprofloxacin	>16	>16	0.25 to >16	5.6	0.9	93.5
Doxycycline	1	16	≤0.12 to 32	66.7	9.2	24.1
Linezolid	2	4	0.25 to 16	87.5	11.6	0.9
Tigecycline	0.12	0.12	≤0.03 to 0.5	NA	NA	NA
Vancomycin	0.5	>32	≤0.12 to >32	80.1	0.5	19.4

[a]NA, MIC breakpoint not applicable.

TABLE 6 MIC distributions for plazomicin against gentamicin-susceptible and gentamicin-nonsusceptible *Staphylococcus aureus* and *Staphylococcus epidermidis*

Organism (no. of isolates) and agent[a]	No. of isolates (cumulative percentage of isolates) with the following plazomicin MIC (μg/ml):								
	≤0.12	0.25	0.5	1	2	4	8	16	>16
Staphylococcus aureus									
Gentamicin S (3,626)	28 (0.8)	262 (8.0)	2,063 (64.9)	1,157 (96.8)	106 (99.7)	10 (100)			
Gentamicin NS (69)		5 (7.2)	29 (49.3)	31 (94.2)	3 (98.6)			1 (100)	
Staphylococcus epidermidis									
Gentamicin S (240)	204 (85.0)	33 (98.8)	3 (100)						
Gentamicin NS (124)	51 (41.1)	64 (92.7)	8 (99.2)		1 (100)				

[a]S, gentamicin susceptible; NS gentamicin nonsusceptible.

therapy for the treatment of infections caused by *S. aureus*, and the exact role of plazomicin for the treatment of *S. aureus* infections remains unclear.

This study has several important limitations that deserve attention. Very few CRE isolates were included, preventing an analysis of plazomicin activity versus this subset. At present, CRE remain uncommon in Canada. Molecular mechanisms of aminoglycoside resistance were also not evaluated. Finally, the plazomicin susceptibility data presented here are likely not applicable to countries where isolates harboring 16S rRNA methyltransferases are more prevalent.

In summary, plazomicin demonstrated potent *in vitro* activity against *Enterobacteriaceae*, including aminoglycoside-nonsusceptible, ESBL-positive, and MDR isolates, tested from a recent 5-year (2013 to 2017) collection of clinical isolates obtained from patients seeking care at Canadian hospitals. These data, in addition to data from recent clinical trials, support a possible role for plazomicin in the treatment of infections due to *Enterobacteriaceae*, including those caused by MDR isolates.

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