

In Vitro Activity of ACHN-490 against Recent Respiratory Tract Pathogens

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Revised Abstract

Introduction: Plazomicin (ACHN-490), a broad-spectrum aminoglycoside with differentiated activity against multi-drug resistant *Enterobacteriaceae*, including carbapenemase-producing strains, is being developed as a first-line treatment for resistant bacterial pathogens. This study evaluated the *in vitro* efficacy of plazomicin and several comparators versus respiratory tract infection (RTI) pathogens from the US and 5 other countries with relatively high antimicrobial resistance rates. **Methods:** 1,026 recent (2007-2009) RTI isolates (US 572, Argentina 216, Greece 101, Turkey 57, India 46, and Brazil 34) were evaluated. Species included *E. coli* (214, including 19 ESBL-positive), *K. pneumoniae* (210, including 54 ESBL-positive), *A. baumannii* (201), *P. aeruginosa* (200), *S. aureus* (50 MRSA, 50 MSSA), *Enterobacter cloacae* (64), and *E. aerogenes* (37). Other than the MRSA and MSSA, isolates were selected without regard for their antimicrobial susceptibility.

Susceptibility of isolates to plazomicin, amikacin, aztreonam, cefepime, ciprofloxacin, daptomycin (S. aureus only), gentamicin, imipenem, piperacillin-tazobactam, tigecycline, and tobramycin was determined by broth microdilution following Clinical and Laboratory Standards Institute (CLSI) guidelines [5].

Quality control was conducted following CLSI guidelines [6].

MIC_{50/90} values were determined for each species, by drug and by country.

Species	n	MIC _{50/90}										
		Plz	Ak	Azt	Cpe	Cp	Dap	Gm	Imp	PT	Tig	Tob
<i>A. baumannii</i>	201	4/64	32/256	>16/16	>8/16	>2/2	na	32/32	>8/8	>64/64	2/4	4/32
<i>E. aerogenes</i>	37	0.5/1	1/2	≤1/16	≤0.5/1	≤0.12/2	na	≤0.25/0.5	1/1	4/64	1/2	0.5/1
<i>E. cloacae</i>	64	≤0.25/0.5	1/4	≤1/16	≤0.5/16	≤0.12/2	na	≤0.25/8	0.5/1	4/64	1/2	0.5/16
<i>E. coli</i>	214	1/2	4/8	≤1/16	≤0.5/16	0.25/2	na	1/32	≤0.25/0.5	4/64	0.5/1	1/16
<i>K. pneumoniae</i>	210	≤0.25/0.5	1/16	≤1/16	≤0.5/16	≤0.12/2	na	≤0.25/32	≤0.25/1	8/64	2/4	0.5/32
<i>P. aeruginosa</i>	200	8/16	4/64	8/16	4/16	0.25/2	na	2/32	2/8	16/64	>4/4	0.5/32
<i>S. aureus</i> , MRSA	50	1/2	16/128	na	>16/16	>2/2	1/1	0.5/32	>8/8	>64/64	0.25/1	>32/32
<i>S. aureus</i> , MSSA	50	1/2	4/8	na	4/4	0.25/0.5	1/1	0.5/1	≤0.25/0.25	2/2	0.25/0.5	0.5/16

Conclusions: Plazomicin MIC_{50/90} values were ± one log₂ dilution of each other for all organisms except *A. baumannii*, and were comparable to Imp and Tig. Plazomicin MIC₉₀ values for all species tested were among the lowest values of all study drugs, particularly against *Enterobacteriaceae* (including ESBL-producers) and MRSA, of which 99% were inhibited by ≤2 mcg/ml of plazomicin. Plazomicin is a promising investigational antimicrobial compound with excellent *in vitro* activity against many RTI pathogens, including those resistant to many presently available drugs.

Introduction

As antimicrobial resistance—often manifested as multi-drug resistance (MDR)—continues to increase in many bacterial species worldwide, the need for new drugs with clinical utility against MDR bacterial pathogens is critical. Extended-spectrum beta-lactamase (ESBL) producing *Enterobacteriaceae*, especially *Escherichia coli* and *Klebsiella pneumoniae*, have become prevalent around the globe. MDR *Acinetobacter baumannii* and *Pseudomonas aeruginosa* have become especially worrisome, because for some strains, there are very few, and in some cases no effective drugs remaining. A much older problem is that of methicillin-resistant *Staphylococcus aureus* (MRSA), though recent approvals of several new antimicrobials with activity against gram-positive pathogens have reduced this concern.

Plazomicin (ACHN-490), a broad-spectrum aminoglycoside that retains activity in the presence of nearly all aminoglycoside-modifying enzymes, is being developed as a first-line treatment for resistant bacterial pathogens. The compound has demonstrated *in vitro* activity against a variety of pathogens, including MRSA, and ESBL- and carbapenemase-producing gram-negative bacteria (except those also harboring 16S rRNA methylases) [1, 2, 3, 4]. This study evaluates the *in vitro* activity of plazomicin and several comparators against pathogens isolated from patients with respiratory tract infection (RTI) from the United States and 5 other countries known to have relatively high antimicrobial resistance rates.

Materials & Methods

- 1,026 isolates collected during 2007, 2008, and 2009 from lower respiratory tract infections in hospitalized patients in 6 countries (United States 572, Argentina 216, Greece 101, Turkey 57, India 46, and Brazil 34) were evaluated. Species included *E. coli* (214, including 19 ESBL-positive), *K. pneumoniae* (210, including 54 ESBL-positive), *A. baumannii* (201), *P. aeruginosa* (200), *S. aureus* (50 MRSA, 50 MSSA), *Enterobacter cloacae* (64), and *E. aerogenes* (37). Other than the MRSA and MSSA, isolates were selected without regard for their antimicrobial susceptibility.
- Susceptibility of isolates to plazomicin, amikacin, aztreonam, cefepime, ciprofloxacin, daptomycin (*S. aureus* only), gentamicin, imipenem, piperacillin-tazobactam, tigecycline, and tobramycin was determined by broth microdilution following Clinical and Laboratory Standards Institute (CLSI) guidelines [5].
- Quality control was conducted following CLSI guidelines [6].
- MIC_{50/90} values were determined for each species, by drug and by country.

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Results

Table 1. Comparison of MIC_{50/90} of all study drugs, by species. Gray shading denotes no CLSI breakpoints defined; no shading denotes value in susceptible category; yellow shading denotes value in intermediate category; red shading denotes value in resistant category.

Species (n)	Plz		Ak		Azt		Cpe		Cp		Dap		Gm		Imp		PT		Tig		Tob	
	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
<i>A. baumannii</i> (201)	4	64	32	256	>16	>16	>16	>16	>2	>2	na	na	32	>32	>8	>8	>64	>64	2	4	4	>32
<i>E. aerogenes</i> (37)	0.5	1	1	2	≤1	>16	≤0.5	1	≤0.12	>2	na	na	≤0.25	0.5	1	1	4	>64	1	2	0.5	1
<i>E. cloacae</i> (64)	0.25	0.5	1	4	≤1	>16	≤0.5	>16	≤0.12	>2	na	na	≤0.25	8	0.5	1	4	>64	1	2	0.5	16
<i>E. coli</i> (214)	1	2	4	8	≤1	16	≤0.5	>16	0.25	>2	na	na	1	>32	≤0.25	0.5	4	>64	0.5	1	1	16
<i>K. pneumoniae</i> (210)	0.25	0.5	1	16	≤1	>16	≤0.5	>16	≤0.12	>2	na	na	≤0.25	>32	≤0.25	1	8	>64	2	4	0.5	32
<i>P. aeruginosa</i> (200)	8	16	4	64	8	>16	4	>16	0.25	>2	na	na	2	>32	2	>8	16	>64	>4	>4	0.5	>32
<i>S. aureus</i> , MRSA (50)	1	2	16	128	na	na	>16	>16	>2	>2	1	1	0.5	>32	>8	>8	>64	>64	0.25	1	>32	>32
<i>S. aureus</i> , MSSA (50)	1	2	4	8	na	na	4	4	0.25	0.5	1	1	0.5	1	≤0.25	≤0.25	2	2	0.25	0.5	0.5	16

Figure 2.

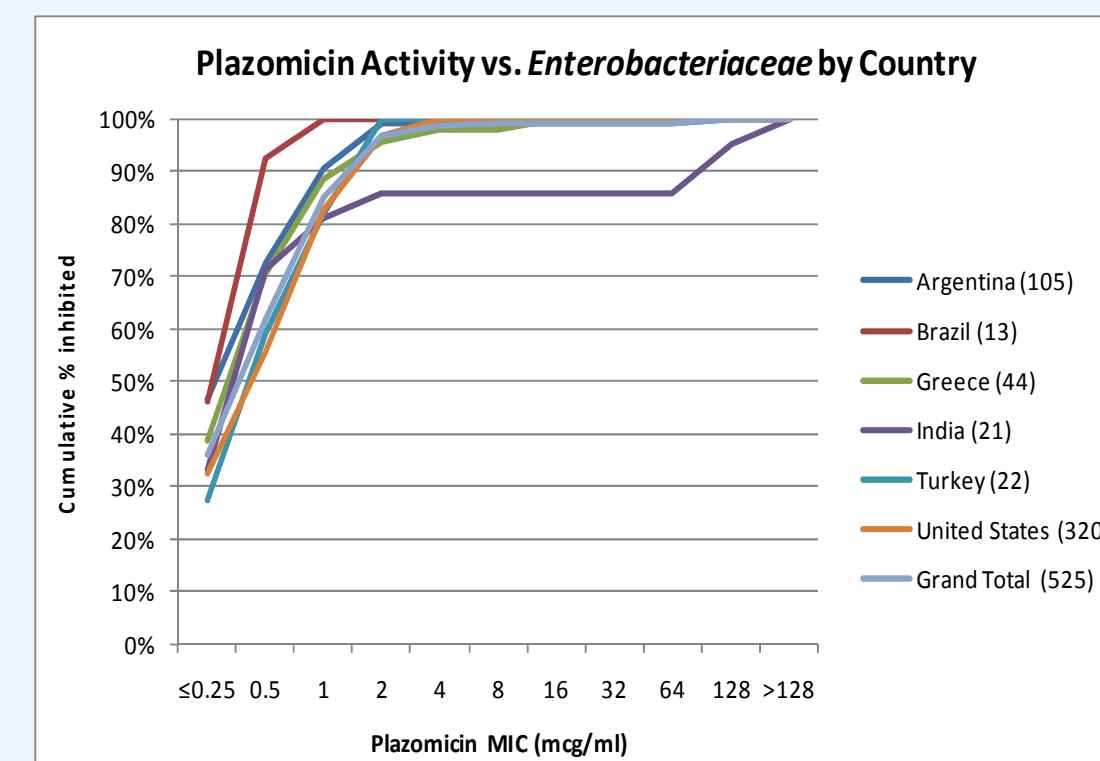


Figure 3.

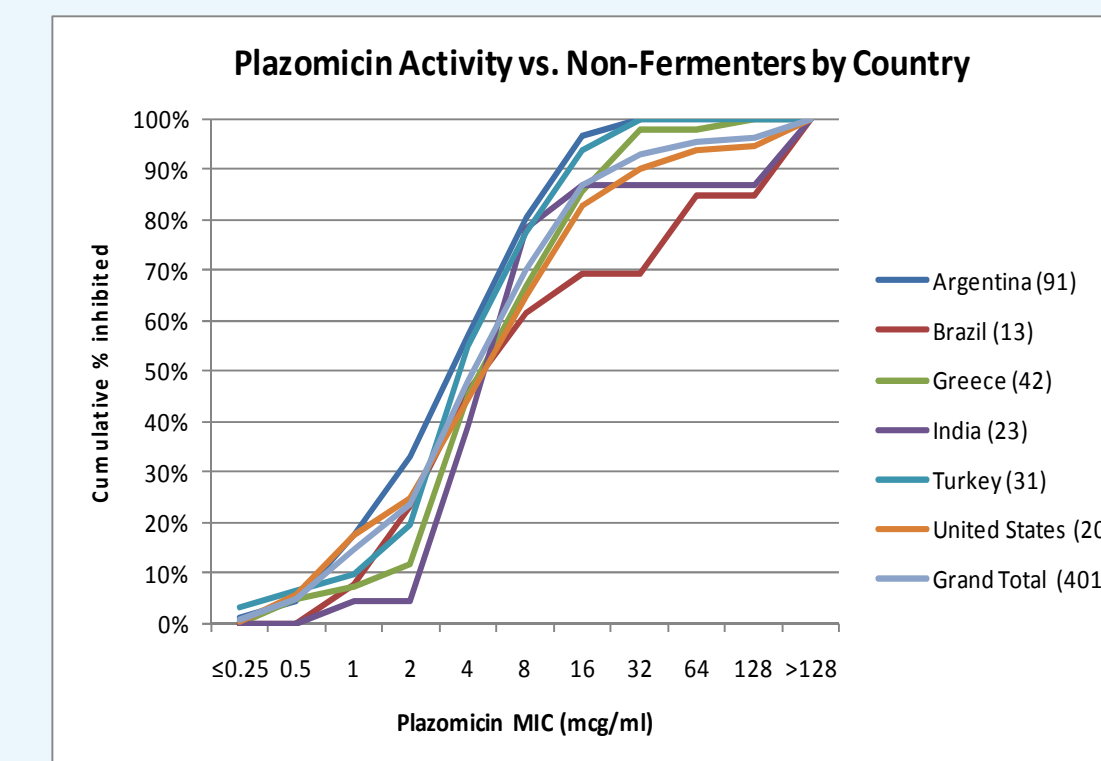
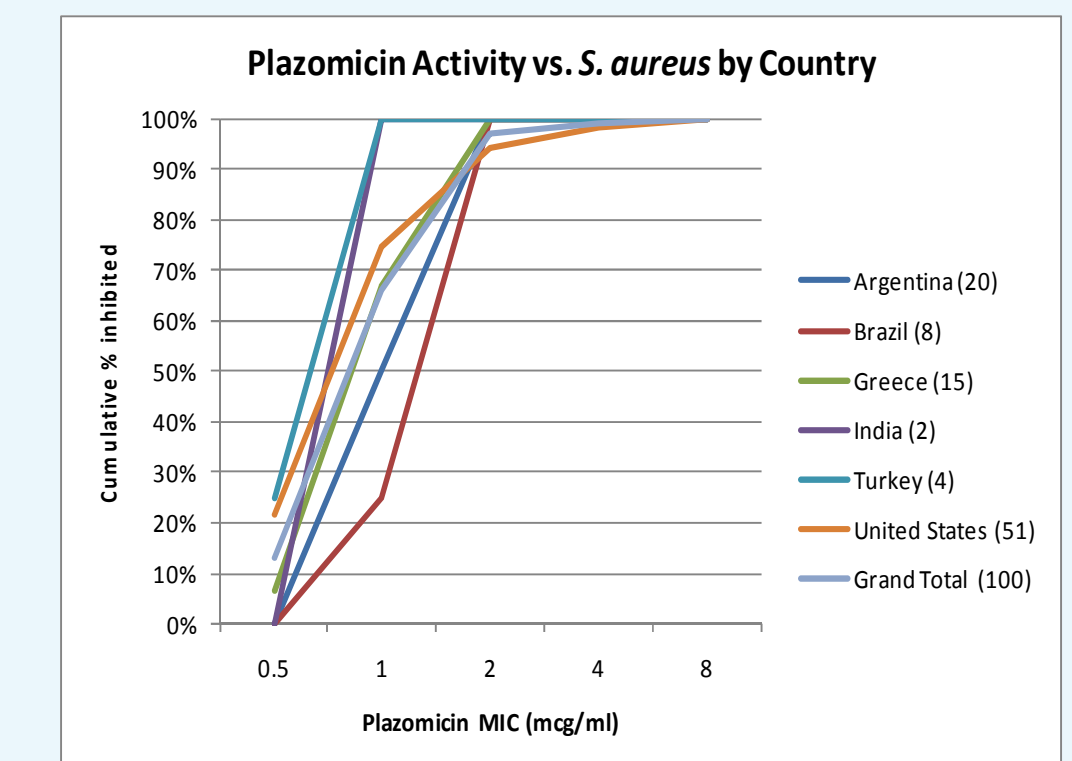


Figure 4.



Conclusions

- With the exception of *A. baumannii*, plazomicin MIC_{50/90} values were within one log₂ dilution of each other for all organism groups, making its activity similar to that of tigecycline and imipenem in that respect.
- The MIC₅₀/MIC₉₀ of plazomicin (no breakpoint yet determined) against *P. aeruginosa* was 8/16 mcg/ml; the MIC₉₀ of each comparator drug was in the resistant range.
- With >90% of *Enterobacteriaceae* (including 73 ESBL-producers) and *S. aureus* (half of which were MRSA) inhibited by ≤2 mcg/ml, plazomicin demonstrated *in vitro* broad-spectrum activity against respiratory tract isolates that warrants consideration for development for the treatment of serious respiratory tract infections.