F-1228

Activity of the First-in-class LpxC Inhibitor ACHN-975 and Comparators Tested against Gram-negative Organisms Including Isolates with Characterized Resistance Mechanisms

M CASTANHEIRA, PR RHOMBERG, RR DIETRICH, RN JONES

JMI Laboratories, North Liberty, Iowa, USA; University of Iowa, Iowa City, Iowa, USA

ICAAC 2013

JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
ph. 319.665.3370, fax 319.665.3371
mariana-castanheira@jmilabs.com

ABSTRACT

Background: Reports of Gram-negative (GN) organisms that are resistant (R) to all clinically available antimicrobials are becoming more common worldwide and a limited number of therapeutic options targeting GNs are in late stages of development. We evaluated the activity of ACHN-975 and comparators tested against 227 GN organisms, including isolates with defined R mechanisms.

Methods: 197 Enterobacteriaceae (ENT) and 30 *P. aeruginosa* (PSA) were susceptibility (S) tested using CLSI broth microdilution methods. ENT included contemporary wildtype (WT) isolates from 24 species, strains producing ESBLs (19 isolates), plasmid mediated (PM) AmpC (12), carbapenemases (CBase; 58 including KPC, NDM, IMP, VIM, SME, NMC-A and OXA-48/-181), PM quinolone (Q) R (22) and isolates displaying elevated tigecycline MICs (eTIG; 11) or ceftazidime-R among AmpC-producing species (CAZ-R; 11). PSA isolates were WT (11), MBL-producers (9) or carbapenem-R MBL-negative (10).

Results: The highest ACHN-975 MIC result among ENT, regardless of the R mechanisms, was 2 µg/mL ($MIC_{50/90}$, 0.5/2 µg/mL; see **Table 1**). ACHN-975 was very active against WT ENT (MIC_{50}, 0.25 µg/mL), and only two-fold less active against CAZ-R, ESBL-, PMAmpC- and CBase-producers (MIC_{50}, 0.5 µg/mL for all groups). eTIG isolates displayed higher ACHN-975 MICs ($MIC_{50/90}$, 2/2 µg/mL). Levofloxacin, tobramycin and cephalosporins had limited activity (<60.0% S overall) against R ENT. TIG (except for eTIG), amikacin (AK) and polymyxin B (PB) were the only comparators showing acceptable activity (75.0-100.0% S). ACHN-975 was very active against PSA ($MIC_{50/90}$, 0.25/0.5 µg/mL) and WT PSA were inhibited by ACHN-975 at ≤0.25 µg/mL. ACHN-975 had similar activity against PSA R subsets ($MIC_{50/90}$, 0.5/1 µg/mL) and highest S rates among comparators were for AK and PB (55.6-70.0 and 100.0% S, respectively).

Conclusions: ACHN-975 seems a promising option for the treatment of ENT and PSA organisms, including isolates with emerging and common R mechanisms.

INTRODUCTION

Antimicrobial resistance among nosocomial and, more recently, community-acquired pathogens is of great concern, and it has compromised the treatment of serious bacterial infections. Among the emerging multidrug-resistant (MDR) organisms, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Enterococcus faecium*, and Gram-negative bacilli (Enterobacteriaceae species, *Pseudomonas aeruginosa* and *Acinetobacter baumannii*) are particularly threatening our ability to manage infections. The advent of vaccines, development of new compounds active against MDR *S. aureus* and *S. pneumoniae,* and the successful implementation of infection control measures are diminishing the burden of the Gram-positive infections; however, fewer options are available for MDR Gram-negative organisms.

Inhibitors of the UDP-3-O-(R-3-hydroxyacyl)-N-acetylglucosamine deacetylase, also known as LpxC, demonstrate promising *in vitro* activity against Gram-negative pathogens. LpxC is a zinc-dependent deacetylase that is part of the lipid A biosynthetic pathway and its inhibition stalls outer membrane biosynthesis in Gram-negative species, including various members of the Enterobacteriaceae family and *P. aeruginosa*. Most LpxC inhibitors reported in the literature have limited spectrum of activity and some of these compounds were shown to have an effect in the immunological system enhancing phagocytosis.

We evaluated the activity of ACHN-975 (chemical structure presented in poster #F-1226), a first-in-class LpxC inhibitor, and comparator antimicrobial agents tested against 227 Enterobacteriaceae and *P. aeruginosa* isolates, including strains with contemporary resistance phenotypes and genotypes.

MATERIALS AND METHODS

Bacterial isolates. A total of 227 Gram-negative clinical isolates were tested and included Enterobacteriaceae species and *P. aeruginosa*. These isolates were collected in 88 hospitals located in North America (101 isolates), Europe (58), Asia-Pacific nations (40) and Latin America (28). Among those, 75 were wildtype contemporary isolates, 108 produced β-lactamase enzymes, 22 carried plasmid-mediated quinolone resistant genes (*qnr*-types or *aac(6)'-Ib-cr*) and 11 tigecycline non-susceptible Enterobacteriaceae. Eleven ceftazidime-resistant isolates from species that might have de-repressed chromosomal cephalosporinases were also selected as putative AmpC-producers. These isolates were collected from bloodstream, respiratory tract, and skin and skin structure infections. Species identification was confirmed by standard biochemical tests, the Vitek2 System (bioMerieux; Hazelwood, Missouri, USA), or sequencing-based methods, when necessary.
Various PCR approaches were used to detect ESBL, plasmidic AmpC, and carbapenemase-encoding genes among Gram-negative bacteria. PCR amplicons were sequenced on both strands and the nucleotide sequences and deduced amino acid sequences were analyzed using the Lasergene software package (DNASTAR; Madison, Wisconsin, USA). Sequences were compared with others available via NCBI/BLAST.

Susceptibility testing. MIC values were determined using Clinical and Laboratory Standards Institute (CLSI) broth microdilution methodology as described in CLSI document M07-A9 (2012). ACHN-975 and comparator agents were tested using cation-adjusted Mueller-Hinton broth defined in the CLSI guidelines. Quality control (QC) ranges and interpretive criteria were those published in CLSI M100-S23 (2013); tested QC strains included *Escherichia coli* ATCC 25922 and *P. aeruginosa* ATCC 27853, and all QC results were within published ranges.

RESULTS

- All Enterobacteriaceae and *P. aeruginosa* isolates were inhibited by ≤2 µg/mL of ACHN-975 (**Table 1** and **Figure 1**) and this compound showed good activity against both groups ($MIC_{50/90}$, 0.5/2 µg/mL for Enterobacteriaceae and 0.25/2 µg/mL for *P. aeruginosa*; **Table 2**).
- ACHN-975 was very active against ESBL-producers ($MIC_{50/90}$, 0.5/2 µg/mL; **Table 2**), including strains producing CTX-M, SHV, TEM and oxacillinase variants. ESBL isolates showed elevated resistance rates against most comparator agents tested and imipenem (100.0% susceptible), tigecycline and amikacin (94.7% susceptible for both) were the agents showing the greatest susceptibility rates against these strains.
- ACHN-975 was two-fold more active against strains producing variants of the plasmid-mediated AmpC CMY, DHA-1 and FOX-5 when compared to ESBL-producers (MIC_{90}, 1 µg/mL; **Tables 1** and **2**).
- *Citrobacter freundii* and *Enterobacter* spp. with putative de-repressed AmpC were inhibited by ACHN-975 at ≤1 µg/mL ($MIC_{50/90}$, 0.5/1 µg/mL). Carbapenems, tigecycline (100.0% susceptible) and amikacin (90.9% susceptible) were the only agents showing >75% susceptibility rates against these organisms (**Table 2**).
- Enterobacteriaceae strains producing different Ambler classes A, B or D carbapenemases were highly resistant to all agents tested (**Table 2**). ACHN-975 displayed good activity against all three groups as follows: $MIC_{50/90}$ was 1/2 µg/mL for KPC-, SME-2- and NMC-A-producing strains (class A), 0.5/1 µg/mL for MβL-producers (Class B) and 1/2 µg/mL for OXA-48/-181-producing strains (Class D).
- ACHN-975 was also active against isolates carrying plasmid-mediated quinolone resistance determinants ($MIC_{50/90}$, 1/1 µg/mL) and *E. coli* and *Klebsiella pneumoniae* strains displaying elevated tigecycline MIC results ($MIC_{50/90}$, 2/2 µg/mL) that displayed high resistant rates against several comparator agents (**Table 2**).
- The activity of ACHN-975 was greater than all other agents tested ($MIC_{50/90}$, 0.12/0.25 µg/mL) against wildtype *P. aeruginosa* strains and this compound displayed remarkable activity against MβL-producing *P. aeruginosa* inhibiting all strains at ≤1 µg/mL (MIC_{50}, 0.5 µg/mL) and carbapenem-resistant MβL-negative *P. aeruginosa* ($MIC_{50/90}$, 0.5/1 µg/mL).

Table 1. MIC distribution and cumulative frequencies of Gram-negative organisms tested against the LpxC inhibitor ACHN-975.

	No. of isolates at ACHN-975 MIC (cumulative %):[a]					
Organism group (no. tested)	≤0.06	0.12	0.25	0.5	1	2
Enterobacteriaceae (197)	2 (1.0)	19 (10.7)	41 (31.5)	64 (64.0)	45 (86.8)	**26 (100.0)**
Wildtype (64)	2 (3.1)	16 (28.1)	23 (64.1)	15 (87.5)	**6 (96.9)**	2 (100.0)
ESBL-producers (19)			5 (26.3)	6 (57.9)	3 (73.7)	**5 (100.0)**
Plasmid-mediated AmpC producers (12)			3 (25.0)	4 (58.3)	**4 (91.7)**	1 (100.0)
Serine-carbapenemase-producers (17)		2 (11.8)	1 (17.6)	5 (47.1)	7 (88.2)	**2 (100.0)**
MβL-producers (22)			3 (13.6)	10 (59.1)	**7 (90.9)**	2 (100.0)
OXA-48/-181-producers (19)			1 (5.3)	8 (47.4)	5 (73.7)	**5 (100.0)**
Plasmid-mediated quinolone resistant isolates (22)			2 (9.1)	8 (45.5)	**10 (90.9)**	2 (100.0)
Ceftazidime-resistant AmpC-producing species (11)[b]			1 (9.1)	7 (72.7)	**3 (100.0)**	
Enterobacteriaceae with tigecycline elevated MIC (11)		1 (9.1)	2 (27.3)	1 (36.4)	0 (36.4)	**7 (100.0)**
P. aeruginosa (30)	1 (3.3)	8 (30.0)	8 (56.7)	8 (83.3)	**5 (100.0)**	
Wildtype (11)	1 (9.1)	7 (72.7)	**3 (100.0)**			
MβL-producers (9)			4 (44.4)	4 (88.9)	**1 (100.0)**	
Carbapenem-resistant non-MβL-producer (10)		1 (10.0)	1 (20.0)	4 (60.0)	**4 (100.0)**	

a. MIC_{50} values are underlined; MIC_{90} values are bolded.
b. *Enterobacter cloacae* and *Citrobacter freundii* that putatively have de-repressed chromosomal AmpC.

Figure 1. Cumulative distribution of ACHN-975 MIC values tested against contemporary Gram-negative isolates.

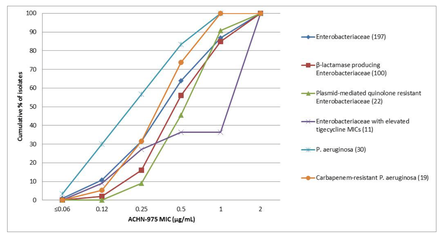

Table 2. In vitro activity of ACHN-975 and comparator agents tested against Gram-negative groups, including contemporary resistant strains.

Organism (no. tested) / Antimicrobial agent	MIC (µg/mL) 50%	MIC (µg/mL) 90%	MIC (µg/mL) Range	% S/ % R[a] CLSI[b]	% S/ % R[a] EUCAST[b]
Enterobacteriaceae (197)					
ACHN-975	0.5	2	≤0.06 – 2	- / -	- / -
Amikacin	2	32	≤0.5 – >64	87.8 / 9.6	81.2 / 12.2
Gentamicin	0.5	>32	≤0.25 – >32	72.1 / 24.4	70.1 / 27.9
Tobramycin	1	>32	≤0.25 – >32	66.0 / 27.9	59.9 / 34.0
Ceftazidime	4	>32	≤0.25 – >32	50.3 / 49.7	46.2 / 49.7
Cefepime	0.5	>32	≤0.25 – >32	70.1 / 28.4	57.9 / 32.5
Piperacillin/tazobactam	8	>64	≤0.5 – >64	56.3 / 32.5	51.8 / 43.7
Imipenem	0.5	16	≤0.12 – >16	68.5 / 20.3	79.7 / 10.2
Tigecycline	0.5	2	0.06 – >4	93.4 / 1.0	88.8 / 6.6
Levofloxacin	0.5	>8	≤0.06 – >8	62.4 / 34.0	58.9 / 37.6
Wildtype (64)					
ACHN-975	0.25	1	≤0.06 – 2	- / -	- / -
Amikacin	1	2	≤0.5 – 16	100.0 / 0.0	98.4 / 0.0
Gentamicin	0.5	1	≤0.25 – >32	96.9 / 3.1	95.3 / 3.1
Tobramycin	0.5	2	≤0.25 – 16	96.9 / 1.6	95.3 / 3.1
Ceftazidime	≤0.25	0.5	≤0.25 – 2	100.0 / 0.0	98.4 / 0.0
Cefepime	≤0.25	≤0.25	≤0.25 – 1	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	1	2	≤0.5 – 16	100.0 / 0.0	98.4 / 0.0
Imipenem	0.5	2	≤0.12 – 4	82.8 / 3.1	96.9 / 0.0
Tigecycline	0.25	2	0.06 – >4	96.9 / 1.6	89.1 / 3.1
Levofloxacin	≤0.06	0.5	≤0.06 – >8	93.8 / 3.1	90.6 / 6.3
ESBL-producers (19)					
ACHN-975	0.5	2	0.25 – 2	- / -	- / -
Amikacin	2	16	≤0.5 – 32	94.7 / 0.0	89.5 / 5.3
Gentamicin	0.5	32	≤0.25 – >32	63.2 / 21.1	57.9 / 36.8
Tobramycin	4	32	≤0.25 – >32	52.6 / 31.6	47.4 / 47.4
Ceftazidime	32	>32	≤0.25 – >32	42.1 / 57.9	21.1 / 57.9
Piperacillin/tazobactam	64	>64	1 – >64	36.8 / 36.8	36.8 / 63.2
Imipenem	≤0.12	0.25	≤0.12 – 1	100.0 / 0.0	100.0 / 0.0
Doripenem	≤0.12	≤0.12	≤0.12 – 2	94.7 / 0.0	94.7 / 0.0
Tigecycline	0.25	2	0.12 – 4	94.7 / 0.0	89.5 / 5.3
Levofloxacin	8	>8	≤0.06 – >8	42.1 / 57.9	31.6 / 57.9
Plasmid-mediated AmpC producers (12)					
ACHN-975	0.5	1	0.25 – 2	- / -	- / -
Amikacin	2	16	1 – 16	100.0 / 0.0	83.3 / 0.0
Gentamicin	0.5	16	≤0.25 – >32	75.0 / 25.0	75.0 / 25.0
Tobramycin	0.5	32	≤0.25 – >32	75.0 / 25.0	75.0 / 25.0
Ceftazidime	>32	>32	16 – >32	0.0 / 100.0	0.0 / 100.0
Cefepime	0.5	0.5	≤0.25 – 2	100.0 / 0.0	91.7 / 0.0
Piperacillin/tazobactam	8	32	2 – >64	58.3 / 8.3	50.0 / 41.7
Imipenem	0.25	0.5	≤0.12 – 1	100.0 / 0.0	100.0 / 0.0
Tigecycline	0.25	0.5	0.12 – 0.5	100.0 / 0.0	100.0 / 0.0
Levofloxacin	0.5	>8	≤0.06 – >8	58.3 / 41.7	58.3 / 41.7
Serine-carbapenemase-producers (17)					
ACHN-975	1	2	0.12 – 2	- / -	- / -
Amikacin	2	64	≤0.5 – >64	76.5 / 11.8	76.5 / 23.5
Gentamicin	8	>32	≤0.25 – >32	47.1 / 41.2	41.2 / 52.9
Tobramycin	16	>32	0.5 – >32	41.2 / 52.9	35.3 / 58.8
Ceftazidime	>32	>32	≤0.25 – >32	23.5 / 76.5	17.6 / 76.5
Cefepime	>32	>32	≤0.25 – >32	35.3 / 64.7	23.5 / 70.6
Piperacillin/tazobactam	>64	>64	≤0.5 – >64	17.6 / 64.7	17.6 / 82.4
Imipenem	16	>16	1 – >16	5.9 / 94.1	5.9 / 58.8
Tigecycline	0.5	1	0.12 – 2	100.0 / 0.0	94.1 / 0.0
Levofloxacin	8	>8	≤0.06 – >8	41.2 / 52.9	35.3 / 58.8
MβL-producers (22)					
ACHN-975	0.5	1	0.25 – 2	- / -	- / -
Amikacin	>64	>64	1 – >64	40.9 / 59.1	27.3 / 59.1
Gentamicin	>32	>32	0.5 – >32	40.9 / 59.1	40.9 / 59.1
Tobramycin	>32	>32	2 – >32	27.3 / 63.6	4.5 / 72.7
Ceftazidime	>32	>32	32 – >32	0.0 / 100.0	0.0 / 100.0
Piperacillin/tazobactam	>64	>64	2 – >64	4.5 / 72.7	4.5 / 95.5
Imipenem	4	>16	0.5 – >16	13.6 / 68.2	31.8 / 27.3
Doripenem	16	>16	1 – >16	13.6 / 77.3	13.6 / 72.7
Tigecycline	0.5	1	0.25 – 4	90.9 / 0.0	90.9 / 9.1
Levofloxacin	>8	>8	≤0.06 – >8	40.9 / 54.5	40.9 / 59.1
OXA-48/-181-producers (19)					
ACHN-975	1	2	0.25 – 2	- / -	- / -
Amikacin	4	>64	1 – >64	78.9 / 21.1	57.9 / 21.1
Gentamicin	1	>32	≤0.25 – >32	63.2 / 36.8	63.2 / 36.8
Tobramycin	16	>32	≤0.25 – >32	42.1 / 57.9	42.1 / 57.9
Ceftazidime	>32	>32	≤0.25 – >32	36.8 / 63.2	36.8 / 63.2
Cefepime	>32	>32	≤0.25 – >32	42.1 / 57.9	42.1 / 57.9
Piperacillin/tazobactam	>64	>64	32 – >64	0.0 / 94.7	0.0 / 100.0
Imipenem	2	>16	0.25 – >16	26.3 / 31.6	68.4 / 15.8
Tigecycline	0.5	2	0.12 – 4	94.7 / 0.0	89.5 / 5.3
Levofloxacin	8	>8	≤0.06 – >8	47.4 / 52.6	47.4 / 52.6

Organism (no. tested) / Antimicrobial agent	MIC (µg/mL) 50%	MIC (µg/mL) 90%	MIC (µg/mL) Range	% S/ % R[a] CLSI[b]	% S/ % R[a] EUCAST[b]
Plasmid-mediated quinolone resistant isolates (22)					
ACHN-975	1	1	0.25 – 2	- / -	- / -
Amikacin	2	8	≤0.5 – 16	100.0 / 0.0	95.5 / 0.0
Gentamicin	0.5	>32	≤0.25 – >32	63.6 / 27.3	63.6 / 36.4
Tobramycin	2	>32	≤0.25 – >32	63.6 / 27.3	50.0 / 36.4
Ceftazidime	16	>32	≤0.25 – >32	40.9 / 59.1	40.9 / 59.1
Cefepime	0.5	>32	≤0.25 – >32	72.7 / 22.7	54.5 / 27.3
Piperacillin/tazobactam	4	>64	1 – >64	77.3 / 18.2	63.6 / 22.7
Imipenem	≤0.12	0.5	≤0.12 – 2	95.5 / 0.0	100.0 / 0.0
Tigecycline	0.25	1	0.12 – 2	100.0 / 0.0	95.5 / 0.0
Levofloxacin	4	>8	0.5 – >8	45.5 / 40.9	36.4 / 54.5
Ceftazidime-resistant AmpC-producing species (putative de-repressed AmpC; 11)					
ACHN-975	0.5	1	0.25 – 1	- / -	- / -
Amikacin	1	16	1 – 32	90.9 / 0.0	81.8 / 9.1
Gentamicin	0.5	>32	≤0.25 – >32	72.7 / 27.3	63.6 / 27.3
Tobramycin	0.5	>32	≤0.25 – >32	72.7 / 27.3	63.6 / 27.3
Cefepime	2	32	≤0.25 – >32	81.8 / 18.2	36.4 / 36.4
Piperacillin/tazobactam	64	>64	2 – >64	27.3 / 45.5	18.2 / 72.7
Imipenem	0.5	1	0.25 – 1	100.0 / 0.0	100.0 / 0.0
Doripenem	≤0.12	0.25	≤0.12 – 0.25	100.0 / 0.0	100.0 / 0.0
Tigecycline	0.5	1	0.12 – 1	100.0 / 0.0	100.0 / 0.0
Levofloxacin	0.5	>8	≤0.06 – >8	72.7 / 27.3	72.7 / 27.3
Tigecycline elevated MICs (11)					
ACHN-975	2	2	0.12 – 2	- / -	- / -
Amikacin	2	8	≤0.5 – 32	90.9 / 0.0	90.9 / 9.1
Gentamicin	1	32	≤0.25 – >32	72.7 / 27.3	72.7 / 27.3
Tobramycin	1	16	≤0.25 – >32	54.5 / 18.2	54.5 / 45.5
Ceftazidime	2	>32	≤0.25 – >32	63.6 / 36.4	45.5 / 36.4
Cefepime	1	>32	≤0.25 – >32	72.7 / 27.3	54.5 / 27.3
Piperacillin/tazobactam	8	>64	1 – >64	81.8 / 18.2	54.5 / 18.2
Imipenem	≤0.12	0.5	≤0.12 – 16	90.9 / 9.1	90.9 / 9.1
Doripenem	≤0.12	0.25	≤0.12 – 16	90.9 / 9.1	90.9 / 9.1
Levofloxacin	8	>8	≤0.06 – >8	45.5 / 54.5	45.5 / 54.5
P. aeruginosa (30)					
ACHN-975	0.25	1	≤0.06 – 1	- / -	- / -
Amikacin	8	>64	2 – >64	66.7 / 33.3	63.3 / 33.3
Gentamicin	4	>32	0.5 – >32	53.3 / 43.3	53.3 / 46.7
Tobramycin	1	>32	≤0.25 – >32	53.3 / 46.7	53.3 / 46.7
Ceftazidime	32	>32	1 – >32	40.0 / 53.3	40.0 / 60.0
Piperacillin/tazobactam	16	>64	2 – >64	53.3 / 33.3	53.3 / 46.7
Imipenem	8	>16	0.5 – >16	36.7 / 63.3	36.7 / 50.0
Levofloxacin	>8	>8	0.25 – >8	36.7 / 56.7	36.7 / 63.3
Polymyxin B	1	2	0.5 – 2	100.0 / 0.0	- / -
Wildtype (11)					
ACHN-975	0.12	0.25	≤0.06 – 0.25	- / -	- / -
Amikacin	2	4	2 – 4	100.0 / 0.0	100.0 / 0.0
Gentamicin	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Tobramycin	0.5	0.5	≤0.25 – 1	100.0 / 0.0	100.0 / 0.0
Ceftazidime	2	2	1 – 4	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	4	4	2 – 4	100.0 / 0.0	100.0 / 0.0
Imipenem	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Levofloxacin	0.5	0.5	0.25 – 1	100.0 / 0.0	100.0 / 0.0
Polymyxin B	1	1	0.5 – 2	100.0 / 0.0	- / -
MβL-producing (9)					
ACHN-975	0.5	-	0.25 – 1	- / -	- / -
Amikacin	64	-	8 – >64	22.2 / 77.8	11.1 / 77.8
Gentamicin	>32	-	16 – >32	0.0 / 100.0	0.0 / 100.0
Tobramycin	>32	-	32 – >32	0.0 / 100.0	0.0 / 100.0
Ceftazidime	>32	-	16 – >32	0.0 / 88.9	0.0 / 100.0
Piperacillin/tazobactam	64	-	4 – >64	33.3 / 44.4	33.3 / 66.7
Imipenem	>16	-	16 – >16	0.0 / 100.0	0.0 / 100.0
Levofloxacin	>8	-	4 – >8	0.0 / 88.9	0.0 / 100.0
Polymyxin B	1	-	1 – 2	100.0 / 0.0	- / -
Carbapenem-resistant non-MβL-producing (10)					
ACHN-975	0.5	1	0.12 – 1	- / -	- / -
Amikacin	8	>64	4 – >64	70.0 / 30.0	70.0 / 30.0
Gentamicin	4	>32	4 – >32	50.0 / 40.0	50.0 / 50.0
Tobramycin	1	>32	1 – >32	50.0 / 50.0	50.0 / 50.0
Ceftazidime	32	>32	8 – >32	10.0 / 80.0	10.0 / 90.0
Piperacillin/tazobactam	>64	>64	16 – >64	20.0 / 60.0	20.0 / 80.0
Imipenem	16	>16	8 – >16	0.0 / 100.0	0.0 / 60.0
Levofloxacin	>8	>8	4 – >8	0.0 / 90.0	0.0 / 100.0
Polymyxin B	1	2	0.5 – 2	100.0 / 0.0	- / -

a. S= susceptible; R= resistant.
b. Criteria as published by CLSI [2013] and EUCAST [2013].

CONCLUSIONS

- ACHN-975 was very active against all isolates tested, including subsets of troublesome isolates producing important and worldwide spread resistance mechanisms. This compound displayed remarkable activity against Enterobacteriaceae isolates carrying genes encoding KPC-2 and -3, NDM-1, CTX-M-15, among others.
- ACHN-975 was also active against carbapenem-resistant *P. aeruginosa* with or without carrying MβL enzymes that are usually MDR and could pose a serious challenge to clinically available antimicrobial agents.
- MDR Gram-negative organisms has been highlighted as a problem of great concern and new agents with novel mechanisms of action are urgently needed as a resource to treat organisms that are resistant to most or all clinically available agents. Our results demonstrate that the further development of ACHN-975 is warranted.

ACKNOWLEDGEMENT

This material is based upon work supported by the Defense Threat Reduction Agency under Contract No. HDTRA1-07-C-0079. Any opinions, findings and conclusions or recommendations expressed in this material are those of the presenters and do not necessarily reflect the views of the U.S. Department of Defense.

REFERENCES

1. Bonomo RA (2011). New Delhi metallo-beta-lactamase and multidrug resistance: a global SOS? *Clin Infect Dis* 52: 485-487.
2. Clinical and Laboratory Standards Institute (2012). *M07-A9. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard: ninth edition*. Wayne, PA: CLSI.
3. Clinical and Laboratory Standards Institute (2013). *M100-S23. Performance standards for antimicrobial susceptibility testing: 23rd informational supplement.* Wayne, PA: CLSI.
4. European Committee on Antimicrobial Susceptibility Testing (2013). Breakpoint tables for interpretation of MICs and zone diameters. Version 3.0, January 2013. Available at: http://www.eucast.org/clinical_breakpoints/. Accessed January 1, 2013.
5. Livermore DM (2009). Has the era of untreatable infections arrived? *J Antimicrob Chemother* 64 Suppl 1: i29-i36.
6. Patel G, Bonomo RA (2013). "Stormy waters ahead": Global emergence of carbapenemases. *Front Microbiol* 4: 48.