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In Vitro Activity of a Carbapenem and Novel ß-lactamase Inhibitor Combination (RPX2003/RPX7009) Tested Against Contemporary Populations of Gram-negative Organisms

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Amended Abstract

BACKGROUND: We evaluated the activity of a carbapenem/serine-ß-lactamase inhibitor (BLI) (Biapenem [RPX2003]/RPX7009 [BP/RPX9]) and comparators tested against contemporary Enterobacteriaceae (ENT), *P. aeruginosa* (PSA) and *A. baumannii* (ACB).

METHODS: 702 ENT, 251 PSA and 154 ACB randomly selected contemporary (2010) clinical isolates collected in a global surveillance program were tested against BP/RPX9 (RPX7009 at fixed 4 µg/mL) and comparators using CLSI broth microdilution reference methods. In addition, BP/RPX9 was tested against 60 KPC-producing ENT.

RESULTS: Overall, BP/RPX9 displayed $MIC_{50/90}$ of 0.12/1 µg/mL against ENT (Table) compared to an $MIC_{50/90}$ ≤0.25/>16 µg/mL for FEP and CAZ. Against *E. coli* (155 strains; $MIC_{50/90}$ of 0.06/0.06 µg/mL) BP/RPX9 showed greater activity than imipenem (IMI; $MIC_{50/90}$, 0.12/0.25 µg/mL) and comparable to that of meropenem (MER; $MIC_{50/90}$, ≤0.015/0.03 µg/mL). *Klebsiella* spp. (154 strains; 2 species) displayed higher resistance rates compared to other ENT and BP/RPX9 inhibited 97.4% of isolates at ≤1 µg/mL, whereas IMI and MER inhibited 91.6% at same MIC. BP/RPX9 inhibited 98.3% of 181 *Enterobacter* spp. at 1 µg/mL and the highest MIC was only 4 µg/mL, ≥four-fold lower than the highest IMI or MER result (16 and >32 µg/mL, respectively). *Serratia* spp., *P. mirabilis* and *M. morganii* displayed slightly higher BP/RPX9 MICs compared to other species ($MIC_{50/90}$, 1/1, 2/2 and 1/1 µg/mL, respectively). BP/RPX9 inhibited all 28 *Citrobacter* spp. at ≤0.25 µg/mL and the $MIC_{50/90}$ was 0.06/0.12 µg/mL. BP/RPX9 inhibited 93.3% of the KPC-producers at ≤1 µg/mL, compared to only 8.3% for RPX2003 alone at the same MIC. Against PSA and ACB, BP/RPX9 exhibited MICs comparable to MER and IMI. Antagonism was not noted in the presence of BLI.

CONCLUSIONS: These results demonstrate that the carbapenem/BLI BP/RPX9 is a prime candidate for further development that could increase the treatment options against serious infections, including those caused by BL-producing pathogens, such as KPC-producers that are resistant to most ß-lactams.

Organism (no. tested)	Cumulative % Inhibited at MIC (µg/mL) of BP/RPX9 with BLI at 4 µg/mL: ≤0.25	0.5	1	2	4	≥8
ENT (702)	68.8	78.6	91.7	98.0	100.0	
KPC-producers (60)	75.0	81.7	93.3	96.7	96.7	100.0
PSA (251)	12.7	48.6	63.4	69.3	71.7	100.0
ACB (154)	33.8	38.3	46.1	48.0	49.4	100.0

Introduction

Bacterial isolates resistant to clinically available ß-lactams present a challenge to successful treatment of serious infections. ß-lactamase-mediated resistance, in particular, represents a significant clinical threat because of the mobile nature of the genes encoding these enzymes. Two strategies have been used to restore the utility of ß-lactam compounds: (i) the design/discovery of novel ß-lactam molecules that are refractory to enzymatic inactivation, and (ii) the inhibition of ß-lactamases, thereby allowing the ß-lactam to retain target concentrations.

Carbapenems possess the broadest spectrum of activity and greatest potency against Gram-positive and -negative bacteria among hundreds of different ß-lactam compounds. These antimicrobial agents play a critically important role in the antimicrobial armamentarium due to greater stability to many ß-lactamases. However, several recent studies clearly show that resistance to carbapenems is increasing throughout the world and the recent spread of carbapenem-resistant pathogens, including those producing KPC enzymes, seriously threatens the use of the carbapenem class.

In this study, we evaluated the activity of the carbapenem biapenem combined with a new serine-ß-lactamase inhibitor (RPX7009) and comparator agents tested against a collection of 1107 randomly selected contemporary Gram-negative isolates from hospitals located in 43 different countries. In addition, a subset of 60 KPC-producing Enterobacteriaceae strains was also tested against biapenem with and without RPX7009.

Materials and Methods

BACTERIAL ISOLATES. A total of 1,107 Gram-negative isolates consecutively collected during 2010 and 2011 as part of a global surveillance program were tested. Only one strain per patient infection episode was included in the surveillance program. Isolates were selected from various medical institutions located in four regions (North America, Europe, Latin America and Asia-Pacific) to represent the contemporary frequency distributions of resistance that occurs in those organisms, as follows: *Escherichia coli* (155 strains); *Klebsiella* spp. (154 strains of *K. pneumoniae* and *K. oxytoca*); *Enterobacter* spp. (181 strains of *E. cloacae* [128 strains] and other species); *Serratia marcescens* (102 strains); *Proteus mirabilis* (53 strains); *Citrobacter* spp. (28 strains); *Morganella morganii* (29 strains); *Pseudomonas aeruginosa* (251 strains) and *Acinetobacter baumannii* (154 strains). Additionally, 60 KPC-producing strains (*K. pneumoniae* [34 strains], *E. coli* [15], *K. oxytoca* [10] and *R. planticola* [1]) were tested.

SUSCEPTIBILITY TESTING. MIC values were determined using Clinical and Laboratory Standards Institute (CLSI) broth microdilution methodology as described in CLSI document M07-A9 (2012). Biapenem with and without the ß-lactamase inhibitor RPX7009 (at a fixed concentration of 4 µg/mL) and comparator agents were tested using cation-adjusted Mueller-Hinton broth as previously described. Quality control (QC) ranges and interpretive criteria were those published in CLSI M100-S22 (2012); tested QC strains included *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853 and KPC-producing *K. pneumoniae* BAA 1705, and all QC results were within published ranges.

Results

- Biapenem/RPX7009 displayed good activity against 702 Enterobacteriaceae isolates, inhibiting 91.6% (Table 1) of these isolates at the current CLSI breakpoint for imipenem and meropenem (susceptible, ≤1 µg/mL). Biapenem alone inhibited 90.2% of the isolates at the same breakpoint concentration.
- Against the subset of KPC-producing strains, biapenem/RPX7009 was highly active and inhibited 93.3% of the isolates at ≤1 µg/mL, whereas only 8.3% of the isolates were inhibited by biapenem alone at the same concentration.
- Biapenem/RPX7009 inhibited all *E. coli* isolates at ≤2 µg/mL, all *Citrobacter* spp. isolates at ≤0.25 µg/mL and 97.4% of the *Klebsiella* spp. isolates at ≤1 µg/mL.
- Among randomly selected *K. pneumoniae*, there were 11 carbapenem-resistant isolates, seven known to produce KPC enzymes and four that were not screened for carbapenemase-encoding genes, including one strain not inhibited by the combination (MIC for biapenem/RPX7009, >32 µg/mL) from India where a high prevalence of NDM-1-producers have been observed.
- Biapenem/RPX7009 inhibited all *Enterobacter* spp. strains at ≤4 µg/mL and only three isolates displayed MIC values >1 µg/mL for this combination. Using CLSI breakpoints for imipenem and meropenem (susceptible, ≤1 µg/mL), 98.3% of these strains would be considered susceptible to this carbapenem/ß-lactamase inhibitor combination, same rate for doripenem and meropenem (Table 2).
- Against *S. marcescens,* biapenem/RPX7009 inhibited 94.1% of strains at ≤1 µg/mL and 99.0% at ≤2 µg/mL (Table 1), displaying activity similar of that of imipenem (MIC_{90}, 1 µg/mL; Table 2). Meropenem and doripenem inhibited 100.0% of the isolates at their current CLSI breakpoints (Table 2).
- *P. mirabilis* (30.2-31.4% inhibited at ≤1 µg/mL) and *M. morganii* (75.9% inhibited at ≤1 µg/mL) showed higher MIC values to biapenem with and without RPX7009 when compared to other Enterobacteriaceae species (Tables 1 and 2). Against *M. morganii*, biapenem/RPX7009 ($MIC_{50/90}$, 1/2 µg/mL; Table 2) was only two-fold more active than imipenem ($MIC_{50/90}$, 2/4 µg/mL) and results for *P. mirabilis* were identical for biapenem ± RPX7009 and imipenem ($MIC_{50/90}$, 2/4 µg/mL; Table 2).
- Biapenem alone or in combination with RPX7009 inhibited 69.3% of the *P. aeruginosa* isolates at ≤2 µg/mL (Table 1), whereas imipenem, meropenem and doripenem inhibited 65.3, 71.3 and 74.1% of these isolates at the same MIC value, respectively (current CLSI breakpoint; Table 2).
- All agents tested showed limited activity against *A. baumannii* (Table 2). The compound showing the highest susceptibility rate was imipenem (50.6% susceptible), while biapenem ± RPX7009 inhibited 49.4% of the isolates at ≤2 µg/mL (Table 1).

TABLE 1. Frequency Distribution of Bacterial Species Tested Against Biapenem Alone or With the Beta-lactamase Inhibitor RPX7009.

Organism/organism group (no. tested)	No. of isolates at MIC (% of cumulative frequency; µg/mL): ≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32
Enterobacteriaceae (702)												
Biapenem	63 (9.0)	230 (41.7)	125 (59.5)	48 (66.4)	73 (76.8)	94 (90.2)	45 (96.6)	11 (98.1)	1 (98.3)	3 (98.7)	4 (99.3)	5 (100.0)
+ RPX7009 fixed 4 µg/mL	64 (9.1)	271 (47.7)	110 (63.4)	37 (68.7)	69 (78.5)	92 (91.6)	44 (97.9)	14 (99.9)	0 (99.9)	0 (99.9)	0 (99.9)	1 (100.0)
KPC-producing strains (60)												
Biapenem	-[a]	0 (0.0)	0 (0.0)	1 (1.7)	0 (1.7)	4 (8.3)	7 (20.0)	11 (38.3)	10 (55.0)	16 (81.7)	1 (83.3)	10 (100.0)
+ RPX7009 fixed 4 µg/mL	-	38 (63.3)	6 (73.3)	1 (75.0)	4 (81.7)	7 (93.3)	2 (96.7)	0 (96.7)	1 (98.3)	0 (98.3)	0 (98.3)	1 (100.0)
E. coli (155)												
Biapenem	49 (31.6)	96 (93.5)	8 (98.7)	0 (98.7)	0 (98.7)	0 (98.7)	2 (100.0)					
+ RPX7009 fixed 4 µg/mL	47 (30.3)	101 (95.5)	5 (98.7)	0 (98.7)	0 (98.7)	0 (98.7)	2 (100.0)					
Klebsiella spp. (154)												
Biapenem	4 (2.6)	52 (36.3)	45 (65.6)	24 (81.2)	14 (90.3)	2 (91.6)	2 (92.9)	0 (92.9)	0 (92.9)	2 (94.2)	4 (96.7)	5 (100.0)
+ RPX7009 fixed 4 µg/mL	4 (2.6)	66 (45.5)	43 (73.4)	21 (87.0)	13 (95.5)	3 (97.4)	2 (98.7)	1 (99.3)	0 (99.3)	0 (99.3)	0 (99.3)	1 (100.0)
Enterobacter spp. (181)												
Biapenem	7 (3.9)	67 (40.9)	65 (76.8)	19 (87.3)	15 (95.6)	4 (97.8)	2 (98.9)	0 (98.9)	1 (99.4)	1 (100.0)		
+ RPX7009 fixed 4 µg/mL	10 (5.5)	86 (53.0)	57 (84.5)	10 (90.1)	13 (97.2)	2 (98.3)	2 (99.5)	1 (100.0)				
Citrobacter spp. (28)												
Biapenem	3 (10.7)	15 (64.3)	7 (89.3)	2 (96.4)	1 (100.0)							
+ RPX7009 fixed 4 µg/mL	3 (10.7)	18 (75.0)	5 (92.9)	2 (100.0)								
Serratia spp. (102)												
Biapenem				3 (2.9)	36 (35.3)	57 (94.1)	5 (99.0)	1 (100.0)				
+ RPX7009 fixed 4 µg/mL				4 (3.9)	36 (39.2)	56 (94.1)	5 (99.0)	1 (100.0)				
P. mirabilis (53)												
Biapenem					4 (7.5)	12 (30.2)	27 (81.1)	10 (100.0)				
+ RPX7009 fixed 4 µg/mL					4 (9.3)	12 (31.4)	26 (79.2)	11 (100.0)				
M. morganii (29)												
Biapenem					3 (10.3)	19 (75.9)	7 (100.0)					
+ RPX7009 fixed 4 µg/mL					3 (10.3)	19 (75.9)	7 (100.0)					
P. aeruginosa (251)												
Biapenem	1 (0.4)	0 (0.4)	6 (2.8)	21 (11.2)	86 (45.4)	46 (63.8)	14 (69.3)	5 (71.3)	29 (82.9)	16 (91.2)	10 (95.2)	12 (100.0)
+ RPX7009 fixed 4 µg/mL	1 (0.4)	1 (0.8)	8 (4.0)	22 (12.7)	90 (48.6)	37 (63.4)	15 (69.3)	6 (71.7)	29 (83.3)	20 (91.2)	8 (94.4)	14 (100.0)
A. baumannii (154)												
Biapenem			17 (11.0)	35 (33.8)	5 (37.0)	11 (44.2)	6 (48.0)	2 (49.4)	6 (53.3)	11 (60.4)	14 (69.5)	47 (100.0)
+ RPX7009 fixed 4 µg/mL		1 (0.6)	20 (13.6)	31 (33.8)	7 (38.3)	12 (46.1)	3 (48.0)	2 (49.4)	7 (53.9)	11 (61.4)	15 (78.9)	45 (100.0)

a. "-" dilution not tested.

TABLE 2. Activity of Biapenem ± RPX7009 and Comparator Antimicrobial Agents When Tested Against β-lactamase-producing Enterobacteriaceae.

Organism (no. tested)/antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
E. coli (155)					
Biapenem/RPX7009 fixed 4 µg/mL[b]	0.12	1	0.03 – >32	NA[b]	NA
Imipenem	0.25	2	≤0.015 – >32	85.2 / 4.5	95.5 / 1.7
Meropenem	0.03	0.06	≤0.015 – >32	97.7 / 2.3	97.7 / 1.8
Doripenem	0.06	0.25	≤0.015 – >32	97.9 / 2.0	97.9 / 1.7
Ertapenem	≤0.03	0.25	≤0.03 – >4	95.0 / 3.7	95.0 / 3.7
Ceftazidime	0.25	>16	≤0.12 – >16	78.7 / 18.6	74.9 / 21.3
Cefepime	≤0.12	>16	≤0.12 – >16	87.2 / 11.6	81.0 / 14.5
Piperacillin/tazobactam	2	64	≤0.5 – >64	87.2 / 6.0	83.1 / 12.8
Levofloxacin	≤0.06	>4	≤0.06 – >4	81.1 / 16.8	78.6 / 18.9
Amikacin	2	8	≤0.5 – >32	97.0 / 1.7	94.6 / 3.0
Klebsiella spp. (154)					
Biapenem/RPX7009 fixed 4 µg/mL[b]	0.12	0.5	0.03 – >32	NA	NA
Imipenem	0.12	0.5	0.03 – >32	91.6 / 8.4	91.6 / 6.5
Meropenem	0.03	0.06	≤0.015 – >32	91.6 / 8.4	91.6 / 7.1
Doripenem	0.06	0.12	≤0.015 – >32	92.2 / 7.1	92.2 / 7.1
Ertapenem	≤0.03	0.5	≤0.03 – >4	90.3 / 9.1	90.3 / 9.1
Ceftazidime	≤0.12	>16	≤0.12 – >16	74.7 / 21.4	72.7 / 25.3
Cefepime	≤0.12	>16	≤0.12 – >16	77.9 / 20.1	73.4 / 24.0
Piperacillin/tazobactam	2	>64	≤0.5 – >64	83.1 / 13.0	78.6 / 16.9
Levofloxacin	≤0.06	>4	≤0.06 – >4	81.2 / 15.6	78.6 / 18.8
Amikacin	1	16	≤0.5 – >32	91.6 / 4.5	87.0 / 8.4
Enterobacter spp. (181)					
Biapenem/RPX7009 fixed 4 µg/mL[b]	0.06	0.25	0.03 – 4	NA	NA
Imipenem	0.5	1	0.03 – 16	93.4 / 1.1	98.9 / 1.1
Meropenem	0.03	0.06	≤0.015 – >32	98.3 / 1.7	98.3 / 1.1
Doripenem	0.06	0.12	≤0.015 – >32	98.3 / 1.7	98.3 / 0.6
Ertapenem	0.06	1	≤0.03 – >4	89.5 / 6.1	89.5 / 6.1
Ceftazidime	0.5	>16	≤0.12 – >16	68.0 / 29.8	64.6 / 32.0
Cefepime	≤0.12	>16	≤0.12 – >16	87.8 / 11.0	77.3 / 13.3
Piperacillin/tazobactam	2	64	≤0.5 – >64	79.6 / 6.6	72.9 / 20.4
Levofloxacin	≤0.06	2	≤0.06 – >4	90.6 / 8.3	89.5 / 9.4
Amikacin	1	4	≤0.5 – >32	98.9 / 1.1	97.8 / 1.1
Citrobacter spp. (28)					
Biapenem/RPX7009 fixed 4 µg/mL[b]	0.06	0.12	0.03 – 0.25	NA	NA
Imipenem	0.5	1	0.12 – 1	100.0 / 0.0	100.0 / 0.0
Meropenem	0.03	0.06	≤0.015 – 0.12	100.0 / 0.0	100.0 / 0.0
Doripenem	0.03	0.06	≤0.015 – 0.12	100.0 / 0.0	100.0 / 0.0
Ertapenem	≤0.03	0.25	≤0.03 – 0.5	100.0 / 0.0	100.0 / 0.0
Ceftazidime	0.25	>16	≤0.12 – >16	85.7 / 14.3	85.7 / 14.3
Cefepime	≤0.12	0.5	≤0.12 – 8	100.0 / 0.0	96.4 / 3.6
Piperacillin/tazobactam	2	32	1 – >64	89.3 / 3.6	89.3 / 10.7
Levofloxacin	≤0.06	2	≤0.06 – >4	96.4 / 3.6	89.3 / 3.6
Amikacin	1	2	≤0.5 – 4	100.0 / 0.0	100.0 / 0.0
Serratia spp. (102)					
Biapenem/RPX7009 fixed 4 µg/mL[b]	1	1	0.25 – 4	NA	NA
Imipenem	0.5	1	0.12 – 2	93.1 / 0.0	100.0 / 0.0
Meropenem	0.03	0.06	0.03 – 0.5	100.0 / 0.0	100.0 / 0.0
Doripenem	0.12	0.25	0.06 – 1	100.0 / 0.0	100.0 / 0.0
Ertapenem	≤0.03	0.12	≤0.03 – 4	99.0 / 1.0	99.0 / 1.0
Ceftazidime	0.25	2	≤0.12 – >16	92.2 / 5.9	88.2 / 7.8
Cefepime	≤0.12	1	≤0.12 – >16	97.1 / 2.9	91.2 / 5.9
Piperacillin/tazobactam	1	16	≤0.5 – >64	92.2 / 2.9	89.2 / 7.8
Levofloxacin	0.12	2	≤0.06 – >4	92.2 / 4.9	89.2 / 7.8
Amikacin	2	4	1 – >32	97.1 / 2.0	94.1 / 2.9
P. mirabilis (53)					
Biapenem/RPX7009 fixed 4 µg/mL[b]	2	4	0.5 – 4	NA	NA
Imipenem	2	4	0.25 – 4	20.8 / 20.8	79.2 / 0.0
Meropenem	0.06	0.06	0.03 – 0.5	100.0 / 0.0	100.0 / 0.0
Doripenem	0.25	0.25	0.06 – 1	100.0 / 0.0	100.0 / 0.0
Ertapenem	≤0.03	≤0.03	≤0.03 – 0.06	100.0 / 0.0	100.0 / 0.0
Ceftazidime	≤0.12	2	≤0.12 – >16	92.5 / 7.5	88.7 / 7.5
Cefepime	≤0.12	1	≤0.12 – >16	92.5 / 3.8	90.6 / 7.5
Piperacillin/tazobactam	≤0.5	≤0.5	≤0.5 – 4	100.0 / 0.0	100.0 / 0.0
Levofloxacin	≤0.06	>4	≤0.06 – >4	77.4 / 20.8	69.8 / 22.6
Amikacin	4	8	2 – 16	100.0 / 0.0	96.2 / 0.0
M. morganii (29)					
Biapenem/RPX7009 fixed 4 µg/mL[b]	1	2	0.5 – 2	NA	NA
Imipenem	2	4	2 – 4	0.0 / 20.7	79.3 / 0.0
Meropenem	0.12	0.12	0.06 – 0.12	100.0 / 0.0	100.0 / 0.0
Doripenem	0.25	0.5	0.12 – 0.5	100.0 / 0.0	100.0 / 0.0
Ertapenem	≤0.03	0.06	≤0.03 – 0.06	100.0 / 0.0	100.0 / 0.0
Ceftazidime	0.25	16	≤0.12 – >16	75.9 / 17.2	65.5 / 24.1
Cefepime	≤0.12	4	≤0.12 – 16	96.6 / 0.0	89.7 / 6.9
Piperacillin/tazobactam	≤0.5	64	≤0.5 – >64	86.2 / 6.9	86.2 / 13.8
Levofloxacin	≤0.06	>4	≤0.06 – >4	75.9 / 13.8	65.5 / 24.1
Amikacin	2	4	≤0.5 – 32	96.6 / 0.0	96.6 / 3.4
P. aeruginosa (251)					
Biapenem/RPX7009 fixed 4 µg/mL[b]	1	16	0.03 – >32	NA	NA
Imipenem	1	16	0.12 – >32	65.3 / 28.7	71.3 / 18.3
Meropenem	0.5	16	≤0.015 – >32	71.3 / 22.7	71.3 / 16.3
Doripenem	0.5	16	0.03 – >32	74.1 / 18.7	66.1 / 18.7
Ertapenem	>4	>4	0.06 – >4	- / -	- / -
Ceftazidime	2	>16	0.5 – >16	75.7 / 18.3	75.7 / 24.3
Cefepime	4	>16	0.25 – >16	77.7 / 12.7	77.7 / 22.3
Piperacillin/tazobactam	4	>64	≤0.5 – >64	78.1 / 13.9	78.1 / 21.9
Levofloxacin	1	>4	≤0.06 – >4	61.4 / 30.3	56.2 / 38.6
Amikacin	4	>32	≤0.5 – >32	86.1 / 11.2	82.1 / 13.9
A. baumannii (154)					
Biapenem/RPX7009 fixed 4 µg/mL[b]	8	>32	0.06 – >32	NA	NA
Imipenem	4	>32	0.12 – >32	50.6 / 46.8	49.4 / 46.8
Meropenem	8	>32	0.12 – >32	47.4 / 49.4	45.5 / 49.4
Doripenem	8	>32	0.06 – >32	37.7 / -	37.7 / 51.9
Ertapenem	>4	>4	1 – >4	- / -	- / -
Ceftazidime	>16	>16	1 – >16	31.2 / 63.0	- / -
Cefepime	>16	>16	1 – >16	31.2 / 63.0	- / -
Piperacillin/tazobactam	>64	>64	≤0.5 – >64	36.4 / 63.6	- / -
Levofloxacin	>4	>4	≤0.06 – >4	31.8 / 64.9	31.8 / 68.2
Amikacin	16	>32	≤0.5 – >32	51.3 / 45.5	48.1 / 48.7

a. Criteria as published by the CLSI [2012] and EUCAST [2012].
b. NA= Not applicable, as breakpoints for biapenem/RPX7009 have not been established.

Conclusions

- Overall, biapenem/RPX7009 was very active against worldwide, randomly selected, Enterobacteriaceae, particularly against KPC-producing isolates.
- Biapenem MICs were similar or slightly lower when biapenem was tested in combination with 4 µg/mL of RPX7009 against non-carbapenemase producing strains.
- Although carbapenems (including biapenem/RPX7009) were among the most active drugs against *P. aeruginosa* and *A. baumannii*, the activity of all drugs was limited against this particular collection of highly resistant bacteria compared to other bacterial species tested.

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REFERENCES

1. Bale MJ, Jones RN, Erwin ME (1994). Minimum inhibitory concentration quality-control guidelines for biapenem, DU-6859a, FK-037, levofloxacin, grepafloxacin, and ceftizoxime when using various National Committee for Clinical Laboratory Standards susceptibility test methods. Quality Control Study Group. *Diagn Microbiol Infect Dis* 19: 65-68.
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 (2012). *M100-S22. Performance standards for antimicrobial susceptibility testing: 22nd informational supplement.* Wayne, PA: CLSI.
4. European Committee on Antimicrobial Susceptibility Testing (2012). Breakpoint tables for interpretation of MICs and zone diameters. Version 2.0, January 2012. Available at: http://www.eucast.org/clinical_breakpoints/. Accessed January 1, 2012.
5. Hoban DJ, Jones RN, Yamane N, Frei R, Trilla A, Pignatari AC (1993). In vitro activity of three carbapenem antibiotics. Comparative studies with biapenem (L-627), imipenem, and meropenem against aerobic pathogens isolated worldwide. *Diagn Microbiol Infect Dis* 17: 299-305.
6. Perry CM, Ibbotson T (2002). Biapenem. *Drugs* 62: 2221-2234.