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Activity of Biapenem (RPX2003)/RPX7009, a Carbapenem Combined with a Novel ß-lactamase Inhibitor (BLI) Tested Against Clinical Isolates Producing Defined Enzymes

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Amended Abstract

BACKGROUND: Isolates producing ß-lactamase (BL) are prevalent and challenging to antimicrobial therapy. We evaluated biapenem (RPX2003)/RPX7009 (BP/9) activity, a carbapenem/Ambler class A, C and D BLI combination, tested against Enterobacteriaceae (ENT) carrying acquired BLs isolated from blood cultures and *Enterobacter* spp. (ESP) hyperproducing chromosomal (hc) AmpC.

METHODS: 151 blood culture isolates of ENT collected from USA hospitals in 2010 were screened for the presence of BL-encoding genes, and their susceptibility (S) to BP/9 and comparators was tested using CLSI broth microdilution methods. RPX7009 was tested at 4, 8 and 16 µg/mL with biapenem. 22 ESP ceftazidime (CAZ)-resistant (R) and cefepime (FEP)-S, hcAmpC, were also studied. Relative AmpC expression was confirmed by quantitative RT-PCR.

RESULTS: BP/9 had good activity against BL-producing ENT (151 strains; $MIC_{50/90}$, 0.06/0.25 µg/mL; BLI at 4 µg/mL) and 148 (98.0%) strains were inhibited at ≤1 µg/mL. BP/9 had activity similar to meropenem (MER; $MIC_{50/90}$, 0.06/0.12 µg/mL) and two- to four-fold greater than imipenem (IMI; $MIC_{50/90}$, 0.25/0.5 µg/mL). Most isolates were R to CAZ, aztreonam (AZT) and FEP (62.9, 62.3 and 45.0% R, respectively). 75 of 76 CTX-M-producers (most prevalent BL) that were inhibited at ≤0.5 µg/mL of BP/9, were highly R to CAZ, AZT and FEP (67.1, 75.0 and 78.9% R, respectively). All hcAmpC ESP were inhibited by BP/9 at 0.25 µg/mL ($MIC_{50/90}$, 0.06/0.25 µg/mL) that showed greater potency than IMI, MER and FEP ($MIC_{50/90}$, 0.5/1, 0.12/0.25 and 1/4 µg/mL, respectively). All 3 BLI concentrations displayed similar results.

CONCLUSIONS: BP/9 demonstrated good activity against these challenge organisms producing BLs for invasive infections, including isolates having 5 enzymes. Further development of this BLI combination appears warranted.

Organisms (no. tested)	Antimicrobial agent	No. of isolates at MIC (µg/mL)[b] ≤0.03	0.06	0.12	0.25	0.5	1	≥2
ESBL-phenotype strains (151)	Biapenem/RPX7009[a]	21	92	20	**8**	2	5	3
	Imipenem	0	2	69	55	**15**	4	6
	Meropenem	68	56	**16**	6	2		
CTX-M-producers (76)	Biapenem /RPX7009[a]	16	**53**	4	2	0	0	1
	Imipenem	0	1	47	**25**	2	0	1
	Meropenem	38	29	**8**	0	0	0	1
Enterobacter spp. hc AmpC (22)	Biapenem/RPX7009[a]	0	11	8	**3**			
	Imipenem	0	0	0	6	10	**6**	
	Meropenem	0	8	11	**2**	1		

a. RPX7009 tested at fixed 4 µg/mL.
b. MIC_{50} results are underlined and MIC_{90} are in bold.

Introduction

Extended-spectrum ß-lactamases (ESBLs) are plasmid-mediated resistance determinants that confer elevated MIC values to penicillins, cephalosporins and aztreonam. The genes encoding these enzymes are often encountered among members of the Enterobacteriaceae family and strains carrying ESBL-encoding genes are frequently resistant to other antimicrobial agents, such as trimethoprim/sulfamethoxazole, aminoglycosides, tetracyclines and fluoroquinolones. Additionally, the plasmid-mediated AmpC enzymes (Ambler class C cephalosporinases) are closely related in sequence to chromosomal AmpC enzymes from *Enterobacter cloacae*, *Morganella morganii*, *Citrobacter freundii* and *Halfnia alvei*. Most of these enzymes are constitutively expressed and produced at much higher levels than seen for basal AmpC cephalosporinases; however, some of the plasmid-encoded AmpC enzymes are inducible and might pose a greater clinical threat since during therapy the organisms can develop resistance to ß-lactam agents.

The presence of multiple ß-lactamases in a single cephalosporin-resistant isolate has been recognized as an alarming fact since the early detection of ß-lactamases. Although strains reported to produce two to four ß-lactamases were commonly characterized, the recent detection of a single *Klebsiella pneumoniae* strain carrying eight ß-lactamase encoding genes, including a KPC carbapenemase and an inhibitor-resistant TEM variant, emphasizes the ability of these organisms to accumulate multiple resistance determinants. The proliferation of these arrays of enzymes limits the use of ß-lactams (carbapenems and clinically available ß-lactamase inhibitor combinations) as empiric treatment options for Gram-negative infections.

In this study, we evaluated the activity of a carbapenem (biapenem [RPX2003]) combined with a serine-ß-lactamase inhibitor RPX7009 against isolates producing Ambler class A, B, C and D ß-lactamases recovered in the United States (USA) during 2010. Isolates carried a single ß-lactamase or multiple enzymes with combinations of up to five enzymes per organism.

Materials and Methods

BACTERIAL ISOLATES. A total of 151 isolates were derived from 214 ESBL-phenotype isolates collected from blood cultures in USA hospitals during 2010. *E. coli*, *Klebsiella* spp. and *Proteus mirabilis* were selected according to CLSI ESBL phenotypic criteria; and *Enterobacter* spp., *Citrobacter* spp., *Serratia* spp. and indole-positive Proteae displaying cefepime MIC values of ≥2 µg/mL were included in the study. These strains producing at least one ß-lactamase (Table 1) were screened for the presence of various genes encoding ß-lactamases, including: bla_{TEM}, bla_{SHV}, bla_{CTX-M}, bla_{GES}, bla_{VEB}, bla_{PER}, bla_{PSE}, bla_{BEL}, oxacillinases with ESBL spectrum (bla_{OXA-2}-, bla_{OXA-10}- and bla_{OXA-30}-group, bla_{OXA-18} and bla_{OXA-45}), $bla_{CMY-1-49}$, $bla_{FOX-1-7}$, $bla_{ACC-1-4}$, $bla_{ACT-1-7}$, $bla_{DHA-1-3}$, bla_{LAT-1}, $bla_{MIR-1-5}$ and $bla_{MOM-1-7}$. *K. oxytoca* strains were screened for the presence of OXY-encoding genes. Isolates with reduced susceptibility to imipenem or meropenem (MIC, ≥2 µg/mL) were screened for production of the following carbapenemases: bla_{IMP}, bla_{VIM}, bla_{SPM-1}, bla_{KPC}, bla_{SME}, bla_{IMI}, bla_{NMC-A}, bla_{GES} and bla_{OXA-48}.

Additionally, 22 ceftazidime-resistant cefepime-susceptible *Enterobacter* spp. that potentially hyperproduce AmpC were included. To confirm production of AmpC, these strains had DNA-free RNA preparations tested using quantitative real-time PCR (qRT-PCR). Relative quantification of target genes expression was performed in duplicate by normalization to an endogenous reference (16S). The critical threshold cycle (C_T) numbers were determined by the detection system software as the amount of target was given as $2^{-\Delta\Delta T}$, where $\Delta\Delta T$ is the difference between the target and reference gene C_T values.

SUSCEPTIBILITY TESTING. MIC values were determined using Clinical and Laboratory Standards Institute (CLSI) broth microdilution methodology as described in CLSI document M07-A9 (2012). The carbapenem biapenem (concentration range, 0.06-64 µg/mL) and the ß-lactamase inhibitor RPX7009 (concentration range 0.5-32 µg/mL) were tested in a checkerboard configuration 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

- Overall, the activity of biapenem with and without the serine-ß-lactamase inhibitor RPX7009 ($MIC_{50/90}$, 0.06/0.25 µg/mL; Table 2) was very good against 151 Enterobacteriaceae strains with an ESBL-phenotype and 148 strains were inhibited at ≤1 µg/mL (CLSI breakpoints for imipenem and meropenem).
- Most isolates were resistant to ceftazidime, aztreonam, cefepime and ampicillin/sulbactam (62.9, 62.3, 45.0 and 68.2% resistant, respectively; Table 2). Carbapenems, including biapenem ± RPX7009 were the only agents that covered >96% of the isolates tested.
- All *E. coli*, *Enterobacter* spp. and *Serratia* spp. (one) strains carrying Ambler class A ß-lactamases were inhibited by 0.12 µg/mL of biapenem/RPX7009 at 4 µg/mL. The only agents with 100.0% susceptible rates against all these bacterial species were biapenem ± RPX7009 and meropenem (Table 2).
- All but one *K. pneumoniae* had an MIC value for biapenem with RPX7009 below 1 µg/mL (current meropenem CLSI breakpoint). This isolate produced CTX-M-15, OXA-1/-30, SHV-11, TEM-1 and most likely a non-enzymatic carbapenem resistance mechanism, since MIC values for imipenem, meropenem and ertapenem were also elevated (2, >2 and >2 µg/mL, respectively).
- Among 76 CTX-M-producing strains, biapenem/RPX7009 inhibited all but one strain at the current CLSI meropenem breakpoint (Table 2; *K. pneumoniae* above). CTX-M-producing strains were highly resistant to most comparator agents (67.1, 75.0, 78.9 and 68.4% resistant to ceftazidime, aztreonam, cefepime and ampicillin/sulbactam, respectively; Table 2), but biapenem ± RPX7009 was comparable to meropenem and imipenem.
- CMY-producing Enterobacteriaceae were very susceptible to imipenem and meropenem (92.3 and 100.0% susceptible, respectively) when applying current breakpoints. Cefepime was very active against these isolates (92.3% susceptible), but ampicillin/sulbactam, ceftazidime and aztreonam inhibited only 0.0, 7.7 and 30.8% of the strains, respectively (Table 2).
- Biapenem/RPX7009 at 4 µg/mL inhibited all *Enterobacter* spp. that hyperproduced AmpC at 0.25 µg/mL. Imipenem, meropenem and cefepime had >95% coverage against these strains at current CLSI breakpoints (Table 2). Other comparators had limited activity against these isolates (0.0 to 81.8% susceptible).

TABLE 1. β-lactamase Content, Biapenem ± RPX7009 and Ceftazidime MIC Results for 151 Non-carbapenemase Producing Enterobacteriaceae Strains Included in this Study.

ß-lactamase content (number of strains)	Organism	Biapenem MIC (µg/mL) range: alone	+ 4 µg/mL RPX7009	Ceftazidime MIC range (µg/mL):
CMY-2 (5)	*E. coli*	0.06 – 0.12	0.03 – 0.06	8 - >32
CMY-2, TEM-1 (5)	*E. coli*	0.03 – 0.25	0.03 – 0.12	8 - >32
CMY-2, SHV-33 (1)	*K. pneumoniae*	0.25	0.25	>32
CMY-like[a], TEM-1 (1)	*E. coli*	0.03	0.03	8
DHA-1, TEM-1 (1)	*P. mirabilis*	2	2	>32
CTX-M-14 (4)	*E. coli*	0.03 – 0.06	0.03 – 0.06	0.25 - 2
CTX-M-14, CMY-2 (1)	*E. coli*	0.06	0.06	32
CTX-M-14, SHV-11, TEM-1 (3)	*K. pneumoniae*	0.03 – 0.06	0.03 – 0.06	2
CTX-M-14, SHV-63, TEM-1 (1)	*K. pneumoniae*	0.06	0.06	8
CTX-M-14, TEM-1 (4)	*E. coli*	0.03 – 0.12	0.03 – 0.12	0.12 - 4
CTX-M-15 (9)	*E. coli*	0.03 – 0.12	0.03 – 0.12	8 - 32
CTX-M-15, OXA-1/30 (17)	*E. coli*	0.03 – 0.06	0.03 – 0.06	0.5 - 32
CTX-M-15, OXA-1/30, PSE-like (1)	*E. coli*	0.06	0.06	>32
CTX-M-15, OXA-1/30, SHV-1 (1)	*K. pneumoniae*	0.12	0.06	>32
CTX-M-15, OXA-1/30, SHV-1, TEM-1 (1)	*K. pneumoniae*	0.5	0.06	32 - >32
CTX-M-15, OXA-1/30, SHV-11, TEM-1 (5)	*K. pneumoniae*	0.03 – >2	0.03 – 2	4 - >32
CTX-M-15, OXA-1/30, TEM-1 (6)	*E. coli*	0.06	0.06 – 0.12	16 - 32
CTX-M-15, SHV-1 (3)	*K. pneumoniae*	0.06 – 0.12	0.06	8 - >32
CTX-M-15, SHV-1, TEM-1 (5)	*K. pneumoniae*	0.03 – 0.25	0.03 – 0.25	16 - >32
CTX-M-15, SHV-1, TEM-1 (1)	*S. marscecens*	0.06	0.06	>32
CTX-M-15, SHV-11 (2)	*K. pneumoniae*	0.12 – 0.25	0.25	16 - >32
CTX-M-15, TEM-1 (8)	*E. coli*	0.03 – 0.06	0.03 – 0.06	16 - 32
CTX-M-27 (2)	*E. coli*	0.06	0.06	1 - 2
CTX-M-27, OXA-1/30 (1)	*E. coli*	0.06	0.06	8
CTX-M-27, SHV-11, TEM-1 (1)	*E. coli*	0.03	0.03	8
CTX-M-27, TEM-1 (1)	*E. coli*	0.06	0.03	2
CTX-M-91, TEM-1 (1)	*P. mirabilis*	0.12	0.06	0.5
OXA-1/30 (1)	*E. coli*	0.06	0.06	1
OXA-1/30, SHV-7, TEM-1 (1)	*K. pneumoniae*	1	1	>32
OXA-2-like, SHV-1, TEM-1 (1)	*K. pneumoniae*	0.5	0.5	>32
OXA-2-like, SHV-7, TEM-1 (2)	*E. cloacae*	0.06 – 0.12	0.06	>32
OXY-like[a] (7)	*K. oxytoca*	0.06 – 0.25	0.06 – 0.25	0.12 - 2
OXY-like[a], SHV-12, TEM-1 (1)	*K. oxytoca*	0.12	0.12	4
PER-1, SHV-12, TEM-1 (1)	*P. stuartii*	1	1	>32
PSE-like, FOX-5 (1)	*E. cloacae*	0.12	0.12	>32
PSE-like, FOX-5 (1)	*P. mirabilis*	1	1	8
PSE-like, FOX-5 (1)	*K. pneumoniae*	0.12	0.12	32
PSE-like, SHV-11, FOX-5 (1)	*K. pneumoniae*	0.12	0.06	>32
SHV-1 (1)	*K. pneumoniae*	0.06	0.06	0.12
SHV-1, TEM-1 (1)	*K. pneumoniae*	0.06	0.06	>32
SHV-11 (3)	*K. pneumoniae*	0.03 – 0.25	0.03 – 0.12	>32
SHV-11, FOX-5 (1)	*K. pneumoniae*	0.12	0.12	>32
SHV-11, TEM-1 (1)	*K. pneumoniae*	1	1	32 - >32
SHV-11, TEM-155 (1)	*P. mirabilis*	>2	>2	>32
SHV-12, TEM-1 (4)	*K. pneumoniae*	0.12 – 0.5	0.06 – 0.25	>32
SHV-12, TEM-1 (1)	*E. coli*	0.06	0.06	32
SHV-12, TEM-1 (1)	*E. cloacae*	0.12	0.12	>32
SHV-2 (1)	*K. pneumoniae*	0.06	0.06	16
SHV-2, TEM-1 (1)	*K. pneumoniae*	0.12	0.12	1
SHV-27 (1)	*K. pneumoniae*	0.06	0.06	0.25
SHV-30 (2)	*K. pneumoniae*	0.06	0.06	2 - 4
SHV-30 (1)	*E. aerogenes*	0.25	0.12	32
SHV-30 (1)	*E. cloacae*	0.25	0.12	>32
SHV-5 (1)	*E. gergoviae*	0.06	0.06	>32
SHV-5, SHV-11, TEM-1 (1)	*K. pneumoniae*	0.06	0.06	>32
SHV-7, OXA-9, TEM-1 (1)	*E. coli*	0.06	0.06	8
SHV-like[a] (3)	*K. pneumoniae*	0.06 – 0.5	0.06 – 0.5	8 - >32
SHV-like[a], TEM-1 (3)	*K. pneumoniae*	0.06 – 1	0.06 – 1	0.5 - >32
TEM-1 (11)	*E. coli*	0.06	0.06	0.06 - 16
TEM-1 (1)	*E. cloacae*	0.12 – 0.25	0.12	>32
TEM-12 (1)	*E. coli*	0.06	0.06	32

a. New variants that are currently being characterized.

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

Antimicrobial agent (no. of strains)	MIC µg/mL 50%	90%	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
Enterobacteriaceae with ESBL-phenotype (151)					
Biapenem	0.06	0.25	0.03 – >2	98.0 / 1.3[b]	98.7 / 0.0[b]
Biapenem /RPX7009 fixed 4 µg/mL	0.06	0.25	0.03 – >2	98.0 / 0.7[b]	99.3 / 0.0[b]
Imipenem	0.25	0.5	0.06 – >2	96.0 / 1.3	98.7 / 0.0
Meropenem	0.06	0.12	≤0.015 – >2	99.3 / 0.7	99.3 / 0.0
Ertapenem	0.06	0.5	≤0.015 – >2	98.0 / 2.0	98.0 / 2.0
Ceftazidime	>8	>8	≤0.06 – >8	31.1 / 62.9	17.2 / 68.9
Piperacillin/tazobactam	8	>64	≤0.5 – >64	74.8 / 18.5	64.2 / 25.2
Aztreonam	>8	>8	≤0.06 – >8	28.5 / 62.3	15.9 / 62.3
Cefepime	16	>16	≤0.12 – >16	49.0 / 45.0	31.1 / 57.6
Ampicillin/sulbactam	>16	>16	2 – >16	6.6 / 68.2	- / 93.4
Escherichia coli (81)					
Biapenem	0.06	0.06	0.03 – 0.25	100.0 / 0.0[b]	100.0 / 0.0[b]
Biapenem /RPX7009 fixed 4 µg/mL	0.06	0.06	0.03 – 0.12	100.0 / 0.0[b]	100.0 / 0.0[b]
Imipenem	0.12	0.25	0.12 – 2	98.8 / 0.0	100.0 / 0.0
Meropenem	0.03	0.06	≤0.015 – 0.12	100.0 / 0.0	100.0 / 0.0
Ertapenem	0.03	0.12	≤0.015 – 0.5	100.0 / 0.0	100.0 / 0.0
Ceftazidime	>8	>8	≤0.06 – >8	34.6 / 60.5	17.3 / 65.4
Piperacillin/tazobactam	4	32	≤0.5 – >64	87.7 / 7.4	77.8 / 12.3
Aztreonam	>8	>8	≤0.06 – >8	32.1 / 55.6	16.0 / 55.6
Cefepime	>16	>16	≤0.12 – >16	43.2 / 51.9	33.3 / 59.3
Ampicillin/sulbactam	>16	>16	2 – >16	4.9 / 63.0	- / 95.1
Klebsiella spp. (55)					
Biapenem	0.06	0.5	0.03 – >2	98.2 / 1.8[b]	98.2 / 0.0[b]
Biapenem /RPX7009 fixed 4 µg/mL	0.06	0.5	0.03 – 2	98.2 / 0.0[b]	100.0 / 0.0[b]
Imipenem	0.25	0.5	0.06 – 2	98.2 / 0.0	100.0 / 0.0
Meropenem	0.06	0.12	0.03 – >2	98.2 / 1.8	98.2 / 0.0
Ertapenem	0.06	0.5	≤0.015 – >2	98.2 / 1.8	98.2 / 1.8
Ceftazidime	>8	>8	0.12 – >8	32.7 / 60.0	20.0 / 67.3
Piperacillin/tazobactam	8	>64	1 – >64	63.6 / 27.3	50.9 / 36.4
Aztreonam	>8	>8	≤0.06 – >8	25.5 / 67.3	14.5 / 67.3
Cefepime	8	>16	≤0.12 – >16	60.0 / 36.4	32.7 / 50.9
Ampicillin/sulbactam	>16	>16	4 – >16	7.3 / 72.7	- / 92.7
CTX-M-producers (76)					
Biapenem	0.06	0.12	0.03 – >2	98.7 / 1.3[b]	98.7 / 0.0[b]
Biapenem /RPX7009 fixed 4 µg/mL	0.06	0.06	0.03 – 2	98.7 / 0.0[b]	100.0 / 0.0[b]
Imipenem	0.12	0.25	0.06 – 2	98.7 / 0.0	100.0 / 0.0
Meropenem	0.03	0.12	≤0.015 – >2	98.7 / 1.3	98.7 / 0.0
Ertapenem	0.06	0.5	≤0.015 – >2	98.7 / 1.3	98.7 / 1.3
Ceftazidime	>8	>8	0.25 – >8	27.6 / 67.1	9.2 / 72.4
Piperacillin/tazobactam	8	>64	≤0.5 – >64	81.6 / 10.5	69.7 / 18.4
Aztreonam	>8	>8	0.25 – >8	15.8 / 75.0	6.6 / 75.0
Cefepime	>16	>16	0.5 – >16	17.1 / 78.9	7.9 / 88.2
Ampicillin/sulbactam	>16	>16	2 – >16	3.9 / 68.4	- / 96.1
CMY-producers (12)					
Biapenem	0.06	0.25	0.03 – 0.25	100.0 / 0.0[b]	100.0 / 0.0[b]
Biapenem /RPX7009 fixed 4 µg/mL	0.06	0.12	0.03 – 0.25	100.0 / 0.0[b]	100.0 / 0.0[b]
Imipenem	0.25	1	0.12 – 2	92.3 / 0.0	100.0 / 0.0
Meropenem	0.06	0.06	≤0.015 – 0.12	100.0 / 0.0	100.0 / 0.0
Ertapenem	0.12	0.5	≤0.015 – 0.5	100.0 / 0.0	100.0 / 0.0
Ceftazidime	>8	>8	4 – >8	7.7 / 92.3	0.0 / 92.3
Piperacillin/tazobactam	4	>64	1 – >64	76.9 / 23.1	76.9 / 23.1
Aztreonam	8	>8	2 – >8	30.8 / 46.2	0.0 / 46.2
Cefepime	0.25	2	≤0.12 – >16	92.3 / 7.7	84.6 / 7.7
Ampicillin/sulbactam	>16	>16	16 – >16	0.0 / 76.9	- / 100.0
Enterobacter spp. hyperproducing AmpC (22)					
Biapenem	0.12	0.25	0.06 – 0.5	100.0 / 0.0[b]	100.0 / 0.0[b]
Biapenem /RPX7009 fixed 4 µg/mL	0.06	0.25	0.06 – 0.25	100.0 / 0.0[b]	100.0 / 0.0[b]
Imipenem	0.5	1	0.25 – 1	100.0 / 0.0	100.0 / 0.0
Meropenem	0.12	0.25	0.06 – 0.5	100.0 / 0.0	100.0 / 0.0
Ertapenem	0.25	1	≤0.015 – 1	81.8 / 0.0	81.8 / 0.0
Ceftazidime	>8	>8	>8	0.0 / 100.0	0.0 / 100.0
Piperacillin/tazobactam	32	>64	2 – >64	31.8 / 13.6	22.7 / 68.2
Aztreonam	>8	>8	8 – >8	0.0 / 86.4	0.0 / 86.4
Cefepime	1	4	≤0.12 – 16	95.5 / 0.0	63.6 / 4.5
Ampicillin/sulbactam	>16	>16	16 – >16	0.0 / 90.9	- / 100.0

a. Criteria as published by the CLSI [2012] and EUCAST [2012].
b. Meropenem breakpoints were used for comparison purposes.

Conclusions

- Biapenem/RPX7009 displayed excellent activity against these selected enzyme-producing strains, including Ambler class A and D serine ß-lactamases or class C chromosomal cephalosporinases.
- Biapenem alone (or with RPX7009) displayed susceptibility test results comparable to imipenem and/or meropenem against this panel of non-carbapenemase producing Enterobacteriaceae. Most isolates carried multiple ß-lactamases that challenge cephalosporin, penicillin and monobactam antimicrobial agents and these genes are often carried in plasmids also harboring resistance determinants to additional antimicrobial classes.

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