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Worldwide Summary of Doripenem Spectrum and Activity: Potencies Against Enterobacteriaceae (57,724 Isolates)

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Abstract

Background: Doripenem (DOR) is a carbapenem approved in many countries for the treatment of nosocomial pneumonia (NP), ventilator-associated bacterial pneumonia (VABP), complicated intra-abdominal infections (cIAI), and complicated urinary tract infections (cUTI). We report the in vitro antimicrobial activity of DOR tested against prevalent Enterobacteriaceae pathogens isolated worldwide.

Methods: During 2003-2009, a total of 57,724 consecutive, non-duplicate isolates from a variety of infections were collected from the following regions (n countries; n isolates): Asia Pacific (13; 10,167), Europe (15; 21,486), Latin America (5; 7,942), and North America (2; 18,129). Susceptibility (S) testing was performed using CLSI methods (M07-A8, M100-S20-U).

Results: DOR demonstrated very high activity against 57,724 Enterobacteriaceae with >97% of isolates inhibited at DOR MIC of ≤0.25 µg/ml. DOR was very active against ceftazidime (CAZ) non-susceptible (NS) *Escherichia coli* ($MIC_{50/90}$, ≤0.06/≤0.06 µg/ml) and most CAZ-NS *Klebsiella pneumoniae* ($MIC_{50/90}$, ≤0.06/4 µg/ml).

Conclusion: Against this very large global population of geographically and temporally (including contemporary [2009]) diverse collection of isolates, DOR exhibited excellent potency against almost all Enterobacteriaceae collected. This large volume of data supports the use of DOR as empiric therapy for hospitalized patients, in whom carbapenem therapy would be warranted to treat serious, difficult-to-treat infections, such as NP, VABP, cIAI, and cUTI.

Introduction

Empiric antimicrobial therapy in healthcare settings that deal with a high proportion of seriously ill patients is becoming progressively more compromised by dramatic increases in the prevalence of extended spectrum β-lactamase (ESBL)-producing Enterobacteriaceae (primarily *Escherichia coli* and *Klebsiella* spp.), constitutively-expressed chromosomal AmpC (Bush group 1 enzymes in *Enterobacter* spp., *Citrobacter* spp and *Serratia* spp.), serine carbapenemases (primarily KPC in *Klebsiella* spp.), and multidrug-resistant (MDR) nonfermentative Gram-negative bacilli. Resistances to "third"- and "fourth-generation" cephalosporins, β-lactam/β-lactamase inhibitor combinations, fluoroquinolones and aminoglycosides have also become commonplace in various geographic regions, requiring the utilization of carbapenems, glycylcyclines, combination therapies or 'agents of last resort' such as the polymyxins.

As an antimicrobial class, carbapenems are innately stable to most β-lactamases of Ambler class A, C and D, and are widely used for serious infections involving resistant Enterobacteriaceae (including ESBL-producing and AmpC over-expressing isolates), anaerobes, *Pseudomonas aeruginosa* and *Acinetobacter* spp. Doripenem was recently approved in Europe and United States (USA) for treatment of complicated intraabdominal infections (cIAI), complicated urinary tract infections (cUTI) and in Europe and other countries including Turkey for hospital-acquired bacterial pneumonia (HABP) – including ventilator-associated bacterial pneumonia (VABP). The agent has a spectrum and potency versus Gram-positive cocci most similar to that of imipenem, and Gram-negative activity like that of meropenem (e.g. two- to four-fold greater than imipenem). The agent is highly β-lactamase stable, is resistant to inactivation by renal dehydropeptidases and, when compared with several other anti-pseudomonal agents, including other carbapenems, has the lowest rate of spontaneously occurring resistance.

In this study, we report *in vitro* testing results from a very large global collection of Enterobacteriaceae collected between 2003-2009 in the SENTRY Antimicrobial Surveillance Program. Doripenem activity was also compared with that of other β-lactam agents and members of several antimicrobial classes used in the empiric or directed therapy of cIAI, cUTI and HABP (including VABP).

Materials and Methods

Bacterial Strain Collection. During 2003-2009, a total of 57,724 consecutive, non-duplicate enteric pathogens isolated from a variety of infections (including HABP, VABP, cIAI, and cUTI) were collected from 183 medical centers (35 countries) in four geographic regions (Table 1). Species identifications were performed by the submitting laboratories with confirmation performed by the central monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA).

Susceptibility Test Methods. All isolates were tested for susceptibility by reference broth microdilution methods using the Clinical Laboratory Standards Institute recommendations (CLSI; M07-A8, 2009). Susceptibility testing was performed by using validated broth microdilution panels manufactured by TREK Diagnostics Systems/Sensititre (Cleveland, Ohio, USA). Validation of the minimum inhibitory concentration (MIC) values was performed by concurrent testing of CLSI-recommended (M100-S20-U, 2010) quality control (QC) strains, including *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853. Categorical interpretation of comparator MIC values was performed according to CLSI (M100-S20-U, 2010) criteria, when available.

Results

- Doripenem was very active against 57,724 Enterobacteriaceae inhibiting 99% of isolates at a MIC ≤0.5 µg/ml (Table 2). Using current CLSI and EUCAST breakpoints, 99.0 and 98.9-99.1% of all isolates were susceptible to doripenem and meropenem, respectively (Table 3). Using CLSI criteria, slightly lower susceptibilities were observed for imipenem (94.1%) and ertapenem (94.8%). Doripenem, meropenem, and ertapenem were the most potent antimicrobial agents tested, being at least eight-fold more potent than imipenem and at least 16-fold more potent than all other agents.
- Doripenem was very active against *E. coli* (MIC_{90}, ≤0.06 µg/ml, 99.9% susceptible), independent of ESBL phenotype or resistance to ceftazidime or other antimicrobials. Similar activity was found for imipenem and meropenem. Among 2,293 (8.7%) CAZ-NS isolates, 79.5, 76.2, 67.1, 59.5, 11.5, and 6.6% were resistant to levofloxacin, tetracycline, trimethoprim/sulfamethoxazole, cefepime, piperacillin/tazobactam, and ertapenem, respectively (Table 3).
- Among 13,819 *Klebsiella* spp., overall doripenem activity was high with a $MIC_{50/90}$ of ≤0.06/0.12 µg/ml and 97.0% of isolates being susceptible (Table 3). Carbapenem resistance rates in 11,709 *K. pneumoniae* were 2.8, 2.9, 3.0, and 5.5% for doripenem, meropenem, imipenem and ertapenem, respectively. Among 2,939 (25.1%) CAZ-NS isolates the resistance rates were much higher at 11.0, 11.4, 11.6 and 20.8% for doripenem (11.0%), meropenem (11.4%), impipenem (11.6%) and ertapenem (20.8%). Against *Klebsiella* spp., resistance to comparator agents ranged from 13.1% for cefepime to 31.2% for ampicillin/sulbactam and were much higher in ceftazidime-non-susceptible *K. pneumoniae* (Table 3).
- Doripenem was also very active against other Enterobacteriaceae tested with $MIC_{50/90}$ values of ≤0.06/0.12, ≤0.06/≤0.06, 0.12/0.25, 0.25/0.5, 0.12/0.25, ≤0.06/≤0.06 and ≤0.06/0.06 for *Enterobacter* spp., *Citrobacter* spp., *P. mirabilis*, indole-positive *Proteus* spp., *Serratia* spp., and *Salmonella* spp., respectively (Table 3).

Table 1. Distribution of 57,724 Enterobacteriaceae isolates and number of medical centers by geographic region

Region and country	Number of medical centers	Number of isolates
Asia Western Pacific (12 countries)	80	10167
Latin America (4 countries)	12	7942
Europe (14 countries)	34	21486
North America (2 countries)	57	18129

Table 2. Percent distribution of doripenem MIC values for 57,724 Enterobacteriaceae (2003-2009)

	Cumulative % inhibited at doripenem MIC (µg/ml):							
Organism (no. of strains)	≤0.06	0.12	0.25	0.5	1	2	4	8
Enterobacteriaceae (57,724)	83	93	98	99	99	99	99.5	99.7
E. coli (26,052)	99	99	99	99	99.9	99.9	99.9	99.9
CAZ-NS[a] (2,293)	93	97	98	98	99	99	99.7	99.9
K. pneumoniae (11,709)	86	94	95	96	97	97	98	99
CAZ-NS[a] (2,939)	63	78	82	85	87	89	92	96
Enterobacter spp. (7,463)	75	91	96	98	99	99	99.6	99.8
Serratia spp. (3,050)	21	80	97	99	99	99.5	99.6	99.7
Proteus mirabilis (2,749)	21	62	95	99	99.6	99.9	99.9	99.9
Citrobacter spp. (1,371)	93	99	99	99	99.8	99.9	100	-
Indole + proteae (1,287)	11	49	86	98	99.7	99.8	99.9	100
Salmonella spp. (1,270)	91	99	100	-	-	-	-	-

a. Ceftazidime non-susceptible (MIC, >4 µg/ml).

Table 3. Antimicrobial activity of doripenem and comparator agents when tested against non-fermentative and fastidious Gram-negative isolates (2003-2009)

Organism (no. tested)/ Antimicrobial agent	MIC in µg/ml: MIC_{50}	MIC_{90}	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
Enterobacteriaceae[a] (57,724)					
Doripenem	≤0.06	0.12	≤0.06 – >8	99.0 / 0.8	99.0 / 0.5
Imipenem	≤0.5	1	≤0.5 – >8	94.1 / 1.8	98.2 / 0.5
Ertapenem	≤0.06	0.12	≤0.06 – >8	94.8 / 3.1	96.9 / 2.0
Meropenem	≤0.12	≤0.12	≤0.12 – >8	98.9 / 0.9	99.1 / 0.5
Ampicillin	>16	>16	≤1 – >16	26.5 / 68.2	-[b] / 73.5
Ampicillin/sulbactam	16	>16	≤2 – >16	48.8 / 34.2	- / 51.2
Piperacillin/tazobactam	2	32	≤0.5 – >64	88.5 / 6.3	84.7 / 11.5
Cefepime	≤0.12	8	≤0.12 – >16	90.6 / 7.4	85.1 / 11.2
Ceftazidime	≤2	16	≤2 – >16	85.3 / 12.9	81.1 / 14.7
Ceftriaxone	≤0.25	>32	≤0.25 – >32	80.2 / 18.8	80.2 / 18.8
Levofloxacin	≤0.5	>4	≤0.5 – >4	80.4 / 17.3	78.8 / 19.6
Tetracycline	≤2	>8	≤2 – >8	61.5 / 35.1	- / -
Trimethoprim/sulfamethoxazole	≤0.5	>1	≤0.5 – >1	71.4 / 28.6	71.4 / 0.0
E. coli (26,502)					
Doripenem	≤0.06	≤0.06	≤0.06 – >8	99.9 / 0.1	99.9 / <0.1
Imipenem	≤0.5	≤0.5	≤0.5 – >8	99.8 / 0.1	99.9 / <0.1
Ertapenem	≤0.06	≤0.06	≤0.06 – >8	98.6 / 0.7	99.3 / 0.3
Meropenem	≤0.12	≤0.12	≤0.12 – >8	99.9 / 0.1	99.9 / <0.1
Ampicillin	>16	>16	≤1 – >16	41.5 / 57.8	- / 58.5
Ampicillin/sulbactam	16	>16	≤2 – >16	48.5 / 30.5	- / 51.5
Piperacillin/tazobactam	2	8	≤0.5 – >64	93.6 / 2.9	90.2 / 6.4
Cefepime	≤0.12	4	≤0.12 – >16	91.9 / 6.4	88.5 / 9.6
Ceftazidime	≤1	4	≤1 – >16	91.2 / 7.2	87.6 / 8.8
Ceftriaxone	≤0.25	>32	≤0.25 – >32	86.9 / 12.7	86.9 / 12.7
Levofloxacin	≤0.5	>4	≤0.5 – >4	74.0 / 24.0	73.7 / 26.0
Tetracycline	≤2	>8	≤2 – >8	60.4 / 39.1	- / -
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5 – >2	63.1 / 36.9	63.1 / 0.0
CAZ-NS[c] *E. coli* (2,293)					
Doripenem	≤0.06	≤0.06	≤0.06 – >8	98.8 / 0.8	98.8 / 0.3
Imipenem	≤0.5	≤0.5	≤0.5 – >8	98.2 / 1.0	99.0 / 0.2
Ertapenem	≤0.06	0.5	≤0.06 – >8	86.6 / 6.6	93.4 / 2.9
Meropenem	≤0.12	≤0.12	≤0.12 – >8	98.5 / 1.1	98.9 / 0.3
Piperacillin/tazobactam	16	>64	≤0.5 – >64	69.5 / 11.5	47.8 / 30.5
Cefepime	>16	>16	≤0.12 – >16	30.3 / 59.5	18.9 / 75.4
Levofloxacin	>4	>4	≤0.5 – >4	17.3 / 79.5	16.8 / 82.7
Tetracycline	>8	>8	≤2 – >8	23.1 / 76.2	- / -
Trimethoprim/sulfamethoxazole	>2	>2	≤0.5 – >2	32.9 / 67.1	32.9 / 0.0
Klebsiella spp.[d] (13,819)					
Doripenem	≤0.06	0.12	≤0.06 – >8	97.0 / 2.5	97.0 / 1.8
Imipenem	≤0.5	≤0.5	≤0.5 – >8	96.1 / 3.0	97.0 / 1.8
Ertapenem	≤0.06	0.25	≤0.06 – >8	92.3 / 4.9	95.1 / 4.0
Meropenem	≤0.12	≤0.12	≤0.12 – >8	96.8 / 2.6	97.4 / 1.6
Ampicillin/sulbactam	8	>16	≤2 – >16	60.7 / 31.2	- / 39.3
Piperacillin/tazobactam	4	>64	≤0.5 – >64	80.8 / 13.5	75.9 / 19.2
Cefepime	≤0.12	>16	≤0.12 – >16	83.6 / 13.1	76.3 / 18.8
Ceftazidime	≤1	>16	≤1 – >16	77.6 / 20.1	73.6 / 22.4
Ceftriaxone	≤0.25	>32	≤0.25 – >32	72.9 / 26.4	72.9 / 26.4
Levofloxacin	≤0.5	>4	≤0.5 – >4	82.4 / 15.3	80.5 / 17.6
Tetracycline	≤2	>8	≤2 – >8	75.9 / 20.7	- / -
Trimethoprim/sulfamethoxazole	≤0.5	>1	≤0.5 – >1	74.7 / 25.3	74.7 / 0.0
K. pneumoniae (11,709)					
Doripenem	≤0.06	0.12	≤0.06 – >8	96.7 / 2.8	96.7 / 2.0
Imipenem	≤0.5	≤0.5	≤0.5 – >8	96.1 / 3.0	97.0 / 1.8
Ertapenem	≤0.06	0.25	≤0.06 – >8	91.2 / 5.5	94.5 / 4.5
Meropenem	≤0.12	≤0.12	≤0.12 – >8	96.4 / 2.9	97.1 / 1.8
Ampicillin/sulbactam	8	>16	≤2 – >16	60.0 / 32.8	- / 40.0
Piperacillin/tazobactam	4	>64	≤0.5 – >64	80.2 / 13.5	74.7 / 19.8
Cefepime	≤0.12	>16	≤0.12 – >16	81.3 / 15.0	74.1 / 21.3
Ceftazidime	≤1	>16	≤1 – >16	74.9 / 22.6	70.8 / 25.1
Ceftriaxone	≤0.25	>32	≤0.25 – >32	71.2 / 28.2	71.2 / 28.2
Levofloxacin	≤0.5	>4	≤0.5 – >4	80.4 / 17.3	78.6 / 19.6
Tetracycline	≤2	>8	≤2 – >8	73.5 / 23.0	- / -
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5 – >2	72.3 / 27.7	72.3 / 0.0
CAZ-NS[c] *K. pneumoniae* (2,939)					
Doripenem	≤0.06	4	≤0.06 – >8	87.0 / 11.0	87.0 / 7.9
Imipenem	≤0.5	4	≤0.5 – >8	85.7 / 11.6	88.4 / 7.3
Ertapenem	0.12	>8	≤0.06 – >8	66.8 / 20.8	79.2 / 17.1
Meropenem	≤0.12	4	≤0.12 – >8	86.0 / 11.4	88.6 / 7.3
Piperacillin/tazobactam	64	>64	≤0.5 – >64	34.3 / 45.6	23.2 / 65.7
Cefepime	>16	>16	≤0.12 – >16	31.2 / 56.4	11.0 / 75.9
Levofloxacin	>4	>4	≤0.5 – >4	38.0 / 56.5	34.3 / 62.0
Tetracycline	>8	>8	≤2 – >8	23.1 / 76.2	- / -
Trimethoprim/sulfamethoxazole	8	>8	≤2 – >8	48.2 / 45.0	- / -
Tetracycline	>2	>2	≤0.5 – >2	28.8 / 71.2	28.8 / 0.0
Enterobacter spp.[e] (7,463)					
Doripenem	≤0.06	0.12	≤0.06 – >8	98.5 / 0.9	98.5 / 0.4
Imipenem	≤0.5	1	≤0.5 – >8	91.9 / 1.6	98.4 / 0.3
Ertapenem	≤0.06	1	≤0.06 – >8	81.5 / 11.2	88.8 / 6.0
Meropenem	≤0.12	≤0.12	≤0.12 – >8	98.4 / 1.2	98.8 / 0.3
Ampicillin/sulbactam	>16	>16	≤2 – >16	26.4 / 52.9	- / 73.6
Piperacillin/tazobactam	4	>64	≤0.5 – >64	76.9 / 11.0	71.6 / 23.1
Cefepime	≤0.12	8	≤0.12 – >16	92.0 / 5.9	79.3 / 11.1
Ceftazidime	≤1	>16	≤1 – >16	68.6 / 28.7	63.3 / 31.4
Ceftriaxone	≤0.25	>32	≤0.25 – >32	63.7 / 34.3	63.7 / 34.3
Levofloxacin	≤0.5	>4	≤0.5 – >4	87.2 / 10.4	84.8 / 12.8
Tetracycline	≤2	>8	≤2 – >8	80.1 / 15.1	- / -
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5 – >2	81.8 / 18.2	81.8 / 0.0
Citrobacter spp.[f] (1,371)					
Doripenem	≤0.06	≤0.06	≤0.06 – 4	99.8 / 0.1	99.8 / 0.0
Imipenem	≤0.5	1	≤0.5 – >8	96.5 / 0.3	99.7 / 0.1
Ertapenem	≤0.06	0.25	≤0.06 – 8	95.8 / 2.0	98.0 / 0.9
Meropenem	≤0.12	≤0.12	≤0.12 – 4	99.7 / 0.2	99.8 / 0.0
Ampicillin	>16	>16	≤1 – >16	13.2 / 76.2	- / 86.8
Ampicillin/sulbactam	8	>16	≤2 – >16	62.7 / 29.1	- / 37.3
Piperacillin/tazobactam	2	64	≤0.5 – >64	83.6 / 6.1	78.0 / 16.4
Cefepime	≤0.12	2	≤0.12 – >16	95.4 / 3.6	88.8 / 6.2
Ceftazidime	≤1	>16	≤1 – >16	76.6 / 21.5	72.4 / 23.4
Ceftriaxone	≤0.25	>32	≤0.25 – >32	73.7 / 25.0	73.7 / 25.0
Levofloxacin	≤0.5	2	≤0.5 – >4	90.3 / 7.5	86.7 / 9.7
Tetracycline	≤2	>8	≤2 – >8	83.1 / 14.4	- / -
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5 – >2	83.4 / 16.6	83.4 / 0.0
P. mirabilis (2,749)					
Doripenem	0.12	0.25	≤0.06 – >8	99.6 / 0.1	99.6 / <0.1
Imipenem	1	2	≤0.5 – >8	62.7 / 6.9	93.1 / 0.1
Ertapenem	≤0.06	≤0.06	≤0.06 – >8	99.7 / 0.3	99.7 / 0.3
Meropenem	≤0.12	≤0.12	≤0.12 – 8	99.8 / 0.2	99.8 / 0.0
Ampicillin	2	>16	≤1 – >16	65.8 / 33.7	- / 34.2
Ampicillin/sulbactam	≤2	16	≤2 – >16	81.8 / 9.4	- / 18.2
Piperacillin/tazobactam	≤0.5	1	≤0.5 – >64	99.3 / 0.1	99.0 / 0.7
Cefepime	≤0.12	0.5	≤0.12 – >16	94.1 / 5.0	91.8 / 6.7
Ceftazidime	≤1	≤1	≤1 – >16	96.5 / 2.8	93.9 / 3.5
Ceftriaxone	≤0.25	0.5	≤0.25 – >32	90.8 / 8.1	90.8 / 8.1
Levofloxacin	≤0.5	>4	≤0.5 – >4	81.4 / 14.6	74.9 / 18.6
Tetracycline	>8	>8	≤2 – >8	1.6 / 98.0	- / -
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5 – >2	66.2 / 33.8	66.2 / 0.0
Indole-positive *Proteus* spp.[g] (1,287)					
Doripenem	0.25	0.5	≤0.06 – 8	99.7 / 0.2	99.7 / 0.1
Imipenem	2	4	≤0.5 – >8	35.2 / 22.4	77.6 / 0.1
Ertapenem	≤0.06	≤0.06	≤0.06 – >8	99.4 / 0.6	99.4 / 0.5
Meropenem	≤0.12	≤0.12	≤0.12 – 8	99.6 / 0.2	99.8 / 0.0
Ampicillin	>16	>16	≤1 – >16	9.9 / 87.8	- / 90.1
Ampicillin/sulbactam	16	>16	≤2 – >16	31.5 / 31.8	- / 68.5
Piperacillin/tazobactam	≤0.5	4	≤0.5 – >64	98.4 / 0.7	97.4 / 1.6
Cefepime	≤0.12	1	≤0.12 – >16	93.9 / 4.4	91.3 / 7.2
Ceftazidime	≤1	8	≤1 – >16	88.7 / 7.4	77.4 / 11.3
Ceftriaxone	≤0.25	8	≤0.25 – >32	78.7 / 14.7	78.7 / 14.7
Levofloxacin	≤0.5	>4	≤0.5 – >4	78.2 / 17.1	74.0 / 21.8
Tetracycline	>8	>8	≤2 – >8	36.0 / 56.3	- / -
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5 – >2	72.1 / 27.9	72.1 / 0.0
Serratia spp.[h] (3,050)					
Doripenem	0.12	0.25	≤0.06 – >8	99.2 / 0.5	99.2 / 0.4
Imipenem	1	2	≤0.5 – >8	89.7 / 1.1	98.9 / 0.3
Ertapenem	≤0.06	0.12	≤0.06 – >8	96.9 / 1.9	98.1 / 1.2
Meropenem	≤0.12	≤0.12	≤0.12 – >8	99.3 / 0.6	99.4 / 0.2
Ampicillin	>16	>16	≤1 – >16	6.0 / 85.2	- / 94.0
Ampicillin/sulbactam	>16	>16	≤2 – >16	9.8 / 69.8	- / 90.2
Piperacillin/tazobactam	2	16	≤0.5 – >64	91.5 / 2.2	88.5 / 8.5
Cefepime	≤0.12	0.5	≤0.12 – >16	96.5 / 2.9	92.7 / 4.3
Ceftazidime	≤2	≤2	≤2 – >16	95.0 / 4.0	89.9 / 5.0
Ceftriaxone	≤0.25	16	≤0.25 – >32	82.2 / 15.3	82.2 / 15.3
Levofloxacin	≤0.5	2	≤0.5 – >4	93.6 / 4.1	88.4 / 6.4
Tetracycline	>8	>8	≤2 – >8	6.5 / 66.9	- / -
Trimethoprim/sulfamethoxazole	≤0.5	2	≤0.5 – >2	91.3 / 8.7	91.3 / 0.0
Salmonella spp.[i] (1,270)					
Doripenem	≤0.06	≤0.06	≤0.06 – 0.25	100.0 / 0.0	100.0 / 0.0
Imipenem	≤0.5	≤0.5	≤0.5 – 2	99.9 / 0.0	100.0 / 0.0
Ertapenem	≤0.06	≤0.06	≤0.06 – 2	99.9 / 0.1	99.9 / 0.1
Meropenem	≤0.12	≤0.12	≤0.12 – 0.5	100.0 / 0.0	100.0 / 0.0
Ampicillin	2	>16	≤1 – >16	78.8 / 20.6	- / 21.2
Ampicillin/sulbactam	≤2	>16	≤2 – >16	81.6 / 13.9	- / 18.4
Piperacillin/tazobactam	4	4	≤0.5 – >64	97.6 / 1.7	96.9 / 2.4
Cefepime	≤0.12	≤0.12	≤0.12 – >16	98.7 / 0.5	97.5 / 1.9
Ceftazidime	≤1	≤1	≤1 – >16	98.1 / 1.4	96.8 / 1.9
Ceftriaxone	≤0.25	≤0.25	≤0.25 – >32	97.2 / 2.8	97.2 / 2.8
Levofloxacin	≤0.5	≤0.5	≤0.5 – >4	99.4 / 0.4	99.0 / 0.6
Tetracycline	≤2	>8	≤2 – >8	80.1 / 19.4	- / -
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – >2	91.5 / 8.5	91.5 / 0.0
Shigella spp.[j] (198)					
Doripenem	≤0.06	0.06	≤0.06 – 0.06	100.0 / 0.0	100.0 / 0.0
Imipenem	≤0.5	≤0.5	≤0.5	100.0 / 0.0	100.0 / 0.0
Ertapenem	≤0.06	≤0.06	≤0.06	100.0 / 0.0	100.0 / 0.0
Meropenem	≤0.12	≤0.12	≤0.12	100.0 / 0.0	100.0 / 0.0
Ampicillin	2	>16	≤1 – >16	78.8 / 20.6	- / 21.2
Ampicillin/sulbactam	>16	>16	≤1 – >16	25.8 / 74.2	- / 74.2
Piperacillin/tazobactam	2	4	≤0.5 – 16	100.0 / 0.0	99.5 / 0.0
Cefepime	≤0.12	0.25	≤0.12 – 1	100.0 / 0.0	100.0 / 0.0
Ceftazidime	≤1	≤1	≤1 – 2	100.0 / 0.0	99.5 / 0.0
Ceftriaxone	≤0.25	≤0.25	≤0.25 – 1	100.0 / 0.0	100.0 / 0.0
Levofloxacin	≤0.5	≤0.5	≤0.5 – 1	100.0 / 0.0	100.0 / 0.0
Tetracycline	>8	>8	≤2 – >8	22.3 / 77.2	- / -
Trimethoprim/sulfamethoxazole	>2	>2	≤0.5 – >2	36.9 / 63.1	36.9 / 0.0

a. Criteria as published by the CLSI [2010] and EUCAST [2010].
b. - = No breakpoint has been established.
c. Ceftazidime non-susceptible (MIC >4 µg/ml).
d. Includes: *K. ornithinolytica* (17 isolates), *K. oxytoca* (1924 isolates), *Klebsiella ozaenae* (28 isolates), *Klebsiella planticola* (one isolate), *K. pneumoniae* (11709 isolates), *K. terrigena* (three isolates), and unspeciated *Klebsiella* (137 isolates).
e. Includes: *E. aerogenes* (1384 isolates), *E. amnigenus* (25 isolates), *E. asburiae* (55 isolates), *E. cancerogenus* (14 isolates), *E. cloacae* (5315 isolates), *E. gergoviae* (27 isolates), *E. hormaechei* (14 isolates), *E. intermedius* (nine isolates), *E. sakazakii* (28 isolates), *E. taylorae* (three isolates), and unspeciated *Enterobacter* (589 isolates).
f. Includes: *C. amalonaticus* (38 isolates), *C. braakii* (52 isolates), *C. fameri* (eight isolates), *C. freundii* (810 isolates), *C. koseri* (377 isolates), *C. sedlakii* (three isolates), *C. youngae* (15 isolates), and unspeciated *Citrobacter* (68 isolates).
g. Includes: *Morganella morganii* (694 isolates), *P. vulgaris* (243 isolates), *Providencia alcalifaciens* (two isolates), *Providencia rettgeri* (70 isolates), *Providencia rustigianii* (one isolate), *Providencia stuartii* (143 isolates), unspeciated *Morganella* (six isolates), unspeciated *Proteus* (83 isolates), and unspeciated *Providencia* (45 isolates).
h. Includes: *S. fonticola* (12 isolates), *S. liquefaciens* (87 isolates), *S. marcescens* (2785 isolates), *S. odorifera* (ten isolates), *S. plymuthica* (19 isolates), *S. rubidaea* (16 isolates), and unspeciated *Serratia* (121 isolates).
i. *S. blockley* (one isolate), *S. brandenburg* (six isolates), *S. bruenderup* (one isolate), *S. choleraesuis* (eight isolates), *S. derby* (two isolates), *S. dublin* (four isolates), *S. enterica* (13 isolates), *S. enteritidis* (232 isolates), *S. hadar* (five isolates), *S. heidelberg* (ten isolates), *S. infantis* (two isolates), *S. java* (one isolate), *S. monterideo* (five isolates), *S. newport* (one isolate), *S. panama* (four isolates), *S. paratyphi* (88 isolates), *S. reading* (one isolates), *S. schwarzer grund* (one isolate), *S. stanley* (two isolates), *S. StPaul* (one isolate), *S. typhi* (206 isolates), *S. typhimurium* (73 isolates), *S. virchow* (seven isolates), Group B *Salmonella* (64 isolates), Group C *Salmonella* (17 isolates), Group D *Salmonella* (129 isolates), and unspeciated *Salmonella* (384 isolates).
j. Includes: *S. boydii* (2 isolates), *S. dysenteriae* (one isolate), *S. flexneri* (134 isolates), *S. sonnei* (56 isolates), and unspeciated *Shigella* (5 isolates).

Conclusions

- Doripenem when tested against a very large (n=57,724), geographically diverse collection of contemporary (2003-2009) Enterobacteriaceae clinical isolates exhibited excellent potency against almost all isolates collected, including ceftazidime-non-susceptible phenotype. Doripenem inhibited 99% of isolates at a MIC of ≤0.5 µg/ml (Table 2).
- Against each species or group of species, doripenem demonstrated similar or greater potency than that of other carbapenems tested. Versus the total population, doripenem, meropenem, and ertapenem were the most potent antimicrobial agents and at least eight-fold more potent than imipenem and at least 16-fold more potent than all other agents tested.
- This data define doripenem activity against the vast majority of contemporary Enterobacteriaceae on a **global scale**, and this new carbapenem is potentially useful in empiric therapy decisions to treat hospitalized patients with serious and typically MDR infections, such as HABP, VABP, cIAI, and cUTI.

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