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Doripenem Activity Against a Global Collection of Enterobacteriaceae, Including Isolates Resistant to Extended-Spectrum Agents

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Abstract

Background: Resistant Enterobacteriaceae and nonfermentative bacilli are rendering many broad-spectrum agents ineffective. Doripenem is a recently approved parental carbapenem displaying inherent stability to most β-lactamases. This study compares the activity of doripenem against Enterobacteriaceae, including ESBL- and AmpC-hyperproducing strains.

Methods: Nonduplicate bacterial isolates (32,993) were collected in >60 medical centers participating in the global doripenem surveillance program (2003-2007). Susceptibility testing was performed by the monitoring laboratory using CLSI methods and interpretive criteria (US FDA for doripenem; susceptible, ≤0.5 µg/mL). ESBL production was confirmed by disk approximation or Etest methods; ceftazidime resistance served as a marker for stably de-repressed AmpC expression in *Enterobacter* spp., *Citrobacter* spp., *Serratia* spp., and indole-positive Proteae (not *P. mirabilis* [PM]).

Results: Overall, the Enterobacteriaceae doripenem-susceptiblity rate (≤0.5 µg/mL) was 98.9%. ESBLs were detected in 5.7%, 17.3%, and 4.8% of *E. coli*, *Klebsiella* spp., and *P. mirabilis*, respectively; AmpC-production rates were 16.6%, 23.7%, 2.2%, and 2.7% for *Citrobacter* spp., *Enterobacter* spp., indole-positive Proteae, and *Serratia* spp. ESBL and AmpC enzymes had little impact on doripenem MIC_{50} potencies (up to 2-fold). Sporadic occurrence of Bush group 2f carbapenemases (KPC) among *Klebsiella* spp. was detected along with rare metallo-β-lactamases in other Enterobacteriaceae, elevating carbapenem MICs.

	MIC (µg/mL)		
Organism (no. tested)	**50%**	**90%**	**% S**
Escherichia coli			
All (15,295)	≤0.06	≤0.06	>99.9
ESBL-confirmed (871)	≤0.06	≤0.06	99.5
Klebsiella spp.			
All (7392)	≤0.06	0.12	97.0
ESBL-confirmed (1279)	≤0.06	0.12	97.9
Proteus mirabilis			
All (1519)	0.12	0.25	99.3
ESBL-confirmed (73)	0.12	0.25	98.6
Citrobacter spp.			
All (790)	≤0.06	≤0.06	99.2
Ceftazidime-resistant (131)	≤0.06	0.12	97.7
Enterobacter spp.			
All (4201)	≤0.06	0.12	97.8
Ceftazidime-resistant (995)	0.12	0.5	92.0
Indole-positive Proteae			
All (781)	0.12	0.5	98.6
Ceftazidime-resistant (17)	0.25	0.5	94.1
Serratia spp.			
All (1658)	0.12	0.25	99.1
Ceftazidime-resistant (44)	0.12	0.5	93.2

Conclusions: Overall susceptibility (≤0.5 µg/mL) for doripenem among Enterobacteriaceae strains was 98.9% and 96.5% for strains expressing ESBL- and AmpC enzymes. The increase seen in AmpC- and ESBL-producing Enterobacteriaceae necessitates a greater reliance upon carbapenem empiric therapy; doripenem may represent a new choice for broad-spectrum coverage of these emerging resistant mechanisms.

Introduction

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 nonfermentative gram-negative bacilli are changing the face of empiric antimicrobial therapy in healthcare settings that deal with a high proportion of seriously ill patients. 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 for treatment of complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI) and nosocomial pneumonia, including ventilator-associated pneumonia. In the United States (USA), doripenem was recently approved by the USA Food and Drug Administration (FDA) with indications for cIAI and cUTI, and it is under regulatory review for nosocomial pneumonia. 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 (eg, 2- to 4-fold greater than imipenem). The agent is highly β-lactamase stable, is resistant to inactivation by renal dehydropeptidases, and when compared with several other antipseudomonal agents, including other carbapenems, has the lowest rate of spontaneously occurring resistance.

This report summarizes the activity of doripenem and selected comparator compounds when tested against a large collection of Enterobacteriaceae submitted to a longitudinal (2003-2007) international doripenem surveillance program, with emphasis on rapidly increasing and problematic resistant subsets.

Materials and Methods

Bacterial Strain Collection

A total of 32,993 nonduplicate consecutive clinical isolates of Enterobacteriaceae were submitted from over 60 medical centers located in North America (34.5%), Latin America (16.5%), Europe (42.3%), and Asia-Pacific (6.7%) as part of the Doripenem International Surveillance Program for the years 2003 through 2007. Isolates originated from patients with documented bloodstream, respiratory, skin and soft tissue, and urinary tract infections. The distribution of species and strains reported here are included in Table 1.

Table 1. Antimicrobial Activity of Doripenem Tested Against a Global Collection of Enterobacteriaceae, Including Isolates Expressing Confirmed ESBL or Inferred AmpC Cephalosporinases

	MIC (µg/mL)		Cumulative % Inhibited at MIC (µg/mL)							
Organism (No. Tested)	**50%**	**90%**	**0.06**	**0.12**	**0.25**	**0.5**	**1**	**2**	**4**	**8**
Escherichia coli										
All (15,295)	≤0.06	≤0.06	97	99	>99	>99	>99	>99	>99	>99
ESBL-confirmed (871)	≤0.06	≤0.06	96	99	>99	>99	100	–	–	–
Klebsiella spp.										
All (7392)	≤0.06	0.12	89	95	96	97	97	98	98	>99
ESBL-confirmed (1279)	≤0.06	0.12	79	92	96	98	99	>99	>99	>99
Proteus mirabilis										
All (1519)	0.12	0.25	24	67	96	>99	>99	>99	>99	>99
ESBL-confirmed (73)	0.12	0.25	14	63	96	98	98	100	–	–
Enterobacter spp.										
All (4201)	≤0.06	0.12	75	91	96	98	99	>99	>99	>99
Ceftazidime-resistant (995)	0.12	0.5	38	73	85	92	94	97	98	>99
Citrobacter spp.										
All (790)	≤0.06	≤0.06	94	98	99	>99	>99	100	–	–
Ceftazidime-resistant (131)	≤0.06	0.12	76	95	97	98	98	100	–	–
Indole-positive Proteae										
All (781)	0.12	0.5	14	52	89	99	>99	>99	100	–
Ceftazidime-resistant (17)	0.25	0.5	–	12	53	94	94	100	–	–
Serratia marcescens										
All (1658)	0.12	0.25	24	81	97	>99	>99	>99	>99	>99
Ceftazidime-resistant (44)	0.12	0.5	23	61	86	93	93	95	98	100

Susceptibility Test Methods

All strains were tested by the Clinical and Laboratory Standards Institute (CLSI; formerly NCCLS) broth microdilution method using cation-adjusted Mueller-Hinton broth in validated panels (TREK Diagnostic Systems, Inc., Cleveland, OH) against a variety of antimicrobial agents representing the most common classes and examples of drugs used for the empiric or directed treatment of the indicated pathogen. Interpretation of MIC results was in accordance with CLSI (2008) published criteria; doripenem-susceptible breakpoint for Enterobacteriaceae was that of the USA-FDA (≤0.5 µg/mL). Enterobacteriaceae with elevated MIC values (≥2 µg/mL) for ceftazidime or ceftriaxone or aztreonam were considered as ESBL-producing phenotypes; confirmatory testing was performed using cefotaxime and ceftazidime alone and in combination with clavulanic acid. AmpC production among characteristic species was extrapolated from the ceftazidime resistance rates. Quality control (QC) strains utilized included *E. coli* ATCC 25922 and 35218 and *P. aeruginosa* ATCC 27853. All QC results were within CLSI-specified ranges.

Results

- Overall, doripenem inhibited 98.9% of the tested Enterobacteriaceae (32,993 isolates) recovered from 4 geographic regions (North America, 98.7%; Latin America, 98.5%; Europe, 99.2%; and Asia-Pacific, 98.7%).
- ESBLs were detected in 5.7%, 17.3%, and 4.8% of *E. coli*, *Klebsiella* spp., and *P. mirabilis*, respectively. Stably de-repressed expression of AmpC (ceftazidime resistance) was evident in 16.6%, 23.7%, 2.2%, and 2.7% of *Citrobacter* spp., *Enterobacter* spp., indole-positive Proteae, and *Serratia* spp.
- Doripenem and meropenem were the most active agents against ESBL-confirmed *E. coli* and *Klebsiella* spp. (MIC_{90} values, ≤0.12 µg/mL; Table 1) and were at least 4-fold more potent than ertapenem against both species (Table 2).

Table 2. Activity of Doripenem and Comparator Antimicrobial Agents Tested Against *E. coli*, *Klebsiella* spp., and *P. mirabilis*, Including Confirmed ESBL-producing Strains

	MIC (µg/mL)		% by Category[a]
Organism (No. Tested)/Antimicrobial Agent	**50%**	**90%**	**Susceptible / Resistant**
Escherichia coli (15,295)			
Doripenem	≤0.06	≤0.06	99.9 / –
Imipenem	≤0.5	≤0.5	>99.9 / <0.1
Meropenem	≤0.06	≤0.06	>99.9 / <0.1
Ertapenem	≤0.06	≤0.06	99.9 / 0.1
Piperacillin/tazobactam	2	8	94.5 / 2.5
Ceftriaxone	≤0.25	0.5	91.6 / 7.4
Ceftazidime	≤1	≤1	94.2 / 3.5
Cefepime	≤0.12	0.5	94.2 / 4.7
Ciprofloxacin	≤0.03	>4	80.0 / 19.9
Gentamicin	≤2	>8	88.9 / 10.4
Escherichia coli (ESBL-confirmed; 871)			
Doripenem	≤0.06	≤0.06	99.5 / –
Imipenem	≤0.5	≤0.5	100.0 / 0.0
Meropenem	≤0.06	≤0.06	100.0 / 0.0
Ertapenem	≤0.06	0.25	99.5 / 0.1
Piperacillin/tazobactam	8	>64	70.5 / 12.2
Ceftriaxone	>32	>32	13.9 / 77.5
Ceftazidime	16	>16	40.9 / 37.7
Cefepime	16	>16	40.2 / 47.0
Ciprofloxacin	>4	>4	25.7 / 73.8
Gentamicin	≤2	>8	54.6 / 42.7
Klebsiella spp. (7392)			
Doripenem	≤0.06	0.12	97.0 / –
Imipenem	≤0.5	≤0.5	98.1 / 1.4
Meropenem	≤0.06	≤0.06	98.1 / 1.4
Ertapenem	≤0.06	0.12	97.1 / 2.4
Piperacillin/tazobactam	2	>64	81.5 / 13.6
Ceftriaxone	≤0.25	>32	78.0 / 16.8
Ceftazidime	≤1	>16	81.3 / 14.8
Cefepime	≤0.12	>16	85.6 / 11.6
Ciprofloxacin	≤0.03	>4	84.1 / 14.3
Gentamicin	≤2	>8	82.1 / 15.9
Klebsiella spp. (ESBL-confirmed; 1279)			
Doripenem	≤0.06	0.12	97.9 / –
Imipenem	≤0.5	≤0.5	99.6 / 0.1
Meropenem	≤0.06	≤0.06	99.6 / 0.2
Ertapenem	≤0.06	0.5	97.6 / 1.5
Piperacillin/tazobactam	32	>64	44.6 / 41.5
Ceftriaxone	>32	>32	17.2 / 60.0
Ceftazidime	>16	>16	32.9 / 52.3
Cefepime	8	>16	50.0 / 40.0
Ciprofloxacin	1	>4	51.5 / 44.3
Gentamicin	>8	>8	36.5 / 56.2
Proteus mirabilis (1519 strains)			
Doripenem	0.12	0.25	99.3 / –
Imipenem	1	2	99.5 / 0.1
Meropenem	≤0.06	0.12	100.0 / 0.0
Ertapenem	≤0.06	≤0.06	99.9 / 0.0
Piperacillin/tazobactam	≤0.5	1	99.3 / 0.1
Ceftriaxone	≤0.25	≤0.25	94.1 / 4.2
Ceftazidime	≤1	≤1	98.0 / 1.5
Cefepime	≤0.12	0.25	95.4 / 4.2
Ciprofloxacin	≤0.03	>4	78.8 / 16.1
Gentamicin	≤2	>8	87.9 / 10.7
Proteus mirabilis (ESBL-confirmed; 73 strains)			
Doripenem	0.12	0.25	98.6 / –
Imipenem	1	2	100.0 / 0.0
Meropenem	≤0.06	0.12	100.0 / 0.0
Ertapenem	≤0.06	≤0.06	100.0 / 0.0
Piperacillin/tazobactam	≤0.5	2	98.6 / 0.0
Ceftriaxone	>32	>32	11.0 / 71.2
Ceftazidime	≤1	16	89.0 / 6.8
Cefepime	>16	>16	19.2 / 72.6
Ciprofloxacin	>4	>4	20.5 / 69.9
Gentamicin	>8	>8	37.0 / 58.9

a. Breakpoint criteria are those of CLSI M100-S18 [2008] or the USA-FDA (Doribax® prescribing information); – = no breakpoints established.

- While ertapenem was the most active agent tested against ESBL-producing *P. mirabilis* (MIC_{90}, ≤0.06 µg/mL; Table 2), doripenem and meropenem were 8- and 16-fold more potent than imipenem.
- Doripenem, imipenem, meropenem, and ertapenem were the most active agents tested against *Enterobacter* spp., *Citrobacter* spp., *Serratia* spp., and indole-positive Proteae, inhibiting 98.3%, 99.3%, 99.6%, and 98.1% of isolates, respectively, at USA-FDA published susceptible breakpoints (Table 3).

Table 3. Antimicrobial Activity of Doripenem Against Select Enterobacteriaceae With Stably De-repressed AmpC Production (Ceftazidime-resistant)

	MIC (µg/mL)		% by Category[a]
Organism (No. Tested)/Antimicrobial Agent	**50%**	**90%**	**Susceptible / Resistant**
Enterobacter spp. (4201)			
Doripenem	≤0.06	0.12	97.8 / –
Imipenem	≤0.5	1	99.1 / 0.4
Meropenem	≤0.06	≤0.06	99.4 / 0.3
Ertapenem	≤0.06	1	97.1 / 1.6
Piperacillin/tazobactam	4	>64	76.8 / 11.1
Ceftriaxone	≤0.25	>32	72.4 / 17.7
Ceftazidime	≤1	>16	71.7 / 23.7
Cefepime	≤0.12	8	92.8 / 5.3
Ciprofloxacin	≤0.03	>4	86.0 / 12.2
Gentamicin	≤2	>8	85.5 / 12.6
Enterobacter spp. (ceftazidime-resistant; 995)			
Doripenem	0.12	0.5	92.0 / –
Imipenem	≤0.5	1	96.7 / 1.2
Meropenem	0.12	0.5	98.0 / 1.1
Ertapenem	0.5	4	89.7 / 5.9
Piperacillin/tazobactam	64	>64	18.8 / 42.7
Ceftriaxone	>32	>32	8.3 / 62.8
Cefepime	4	>16	77.9 / 15.9
Ciprofloxacin	0.5	>4	56.5 / 39.7
Gentamicin	≤2	>8	56.7 / 38.2
Citrobacter spp. (790)			
Doripenem	≤0.06	≤0.06	99.2 / –
Imipenem	≤0.5	1	99.7 / 0.1
Meropenem	0.12	0.12	100.0 / 0.0
Ertapenem	≤0.06	0.12	99.5 / 0.1
Piperacillin/tazobactam	2	64	84.3 / 5.9
Ceftriaxone	≤0.25	>32	80.1 / 10.3
Ceftazidime	≤1	>16	80.3 / 16.6
Cefepime	≤0.12	1	95.9 / 2.9
Ciprofloxacin	≤0.03	1	90.2 / 8.3
Gentamicin	≤2	4	90.1 / 8.7
Citrobacter spp. (ceftazidime-resistant; 131)			
Doripenem	≤0.06	0.12	97.7 / –
Imipenem	≤0.5	1	99.2 / 0.0
Meropenem	0.12	0.12	100.0 / 0.0
Ertapenem	0.12	0.5	99.2 / 0.0
Piperacillin/tazobactam	64	>64	26.7 / 29.0
Ceftriaxone	32	>32	3.1 / 44.3
Cefepime	1	>16	85.5 / 10.7
Ciprofloxacin	0.06	>4	73.5 / 24.8
Gentamicin	≤2	>8	75.6 / 22.1
Indole-positive Proteae (781)			
Doripenem	0.12	0.5	98.6 / –
Imipenem	2	4	99.2 / 0.1
Meropenem	0.12	0.12	99.9 / 0.0
Ertapenem	≤0.06	≤0.06	99.6 / 0.0
Piperacillin/tazobactam	≤0.5	4	98.7 / 0.6
Ceftriaxone	≤0.25	4	92.2 / 5.8
Ceftazidime	≤1	4	94.6 / 2.2
Cefepime	≤0.12	1	93.6 / 4.4
Ciprofloxacin	≤0.03	>4	77.8 / 19.0
Gentamicin	≤2	>8	85.1 / 12.5
Indole-positive Proteae (ceftazidime-resistant; 17)			
Doripenem	0.25	0.5	94.1 / –
Imipenem	2	4	94.1 / 0.0
Meropenem	0.12	0.25	100.0 / 0.0
Ertapenem	≤0.06	0.12	100.0 / 0.0
Piperacillin/tazobactam	8	>64	58.8 / 17.6
Ceftriaxone	16	>32	47.1 / 23.5
Cefepime	0.5	>16	76.5 / 11.8
Ciprofloxacin	>4	>4	33.3 / 66.7
Gentamicin	>8	>8	35.3 / 64.7

Table 3. *continued*

	MIC (µg/mL)		% by Category[a]
Organism (No. Tested)/Antimicrobial Agent	**50%**	**90%**	**Susceptible / Resistant**
Serratia spp. (1658)			
Doripenem	0.12	0.25	99.1 / –
Imipenem	≤0.5	1	99.6 / 0.3
Meropenem	0.12	0.12	99.5 / 0.3
Ertapenem	≤0.06	0.12	99.5 / 0.5
Piperacillin/tazobactam	2	16	90.3 / 2.4
Ceftriaxone	≤0.25	8	90.1 / 4.6
Ceftazidime	≤1	2	95.7 / 2.7
Cefepime	≤0.12	0.5	96.4 / 3.2
Ciprofloxacin	0.06	1	91.0 / 6.0
Gentamicin	≤2	4	90.7 / 7.5
Serratia spp. (ceftazidime-resistant; 44)			
Doripenem	0.12	0.5	93.2 / –
Imipenem	1	2	97.7 / 0.0
Meropenem	0.12	0.25	97.7 / 0.3
Ertapenem	≤0.06	0.5	97.7 / 0.0
Piperacillin/tazobactam	8	>64	54.5 / 13.6
Ceftriaxone	>32	>32	6.8 / 52.3
Cefepime	4	>16	72.7 / 27.3
Ciprofloxacin	1	>4	68.4 / 21.1
Gentamicin	>8	>8	31.8 / 56.8

a. Breakpoint criteria are those of CLSI M100-S18 [2008] or the USA-FDA (Doribax® prescribing information); – = no breakpoints established.

- Among constitutive AmpC-producing (ceftazidime-resistant) strains, doripenem and meropenem were 8- to 16-fold more potent than either imipenem or ertapenem (Table 3).
- Sporadic occurrence of Bush group 2f carbapenemases (KPC) among *Klebsiella* spp. was detected along with rare metallo-β-lactamases in other Enterobacteriaceae, resulting in elevated carbapenem MICs among those strains.

Conclusions

- The increases being observed in ESBL- and AmpC-producing enteric species are changing empiric therapy decisions, with greater reliance on carbapenems due to their greater stability to the most commonly encountered β-lactamases.
- Overall, doripenem inhibited 98.9% of tested Enterobacteriaceae at the current USA-FDA breakpoint and 96.5% of strains expressing ESBL and AmpC enzymes were doripenem-susceptible.
- Doripenem may represent an alternative choice for broad-spectrum coverage of prevalent Gram-positive and Gram-negative pathogens, including those with emerging resistance mechanisms that are highly problematic for current therapeutic guidelines.

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