Antimicrobial Activity of Broad-spectrum β-Lactams, Including Doripenem, Tested Against Bloodstream Infection Isolates: A Global Surveillance Report (2003-2005)

Thomas R. Fritsche, Helio S. Sader, and Ronald N. Jones

JMI Laboratories, North Liberty, Iowa, USA

Thomas R. Fritsche, MD, PhD
JMI Laboratories
345 Beaver Kreek Centre, Suite A
North Liberty, IA 52317-9258
Tel: (319) 665-3370 • Fax: (319) 665-3371
E-mail: thomas-fritsche@jmilabs.com

AMENDED ABSTRACT[a]

Background: Bloodstream infections (BSI) require prompt management with targeted antimicrobials for favorable outcomes. We summarize the results of an international surveillance program comparing doripenem (DOR), an investigational broad-spectrum parenteral carbapenem (CARB) in late-stage clinical development, with comparator agents against contemporary BSI pathogens.

Methods: Non-duplicate BSI isolates (29,176) were collected from >60 medical centers in North America (NA), Latin America (LA), and Europe (EU) (2003-2005). Identifications were confirmed by the central monitor and all isolates were susceptibility (S) tested using CLSI methods against DOR, meropenem (MEM), imipenem (IPM), and comparators.

Results: At MIC values of 0.25 for *S. pneumoniae* (SPN), 0.5 for beta-hemolytic streptococci (BHS) and 4 μg/mL for all others (equivalent to peer agents), DOR inhibited >97% of the top 10 pathogens (excluding enterococci) recovered from all sources.

	MIC_{90}/% S		
Organism (no. tested)	**DOR**	**MEM**	**IPM**
S. aureus (OXA-S; 4,652)	≤0.06/100	0.12/100	≤0.12/100
CoNS* (OXA-S; 650)	≤0.06/100	0.12/100	≤0.12/100
SPN (669)	0.25/90	0.5/88	–
BHS (767)	≤0.06/100	≤0.06/100	≤0.12/100
E. coli (EC; 6,432)	≤0.06/100	≤0.06/100	≤0.5/100
Klebsiella spp. (KSP; 2,729)	≤0.06/98	≤0.06/98	≤0.5/98
Enterobacter spp. (1,452)	0.12/>99	0.12/>99	1/>99
Serratia (544)	0.25/98	0.12/98	1/>99
P. aeruginosa (PSA; 1,944)	8/87	>8/82	>8/79
Acinetobacter spp. (713)	>8/78	>8/74	>8/78

*CoNS = coagulase-negative staphylococci.

All CARBs were highly active against leading pathogens producing BSI (exception, enterococci) with DOR being ≥2-fold (MIC_{90}), more active than MEM against SA, CoNS, SPN, and PSA, and 4- to 8-fold more active than IPM against some Enterobacteriaceae. % PSA with DOR/MEM/IPM MIC values ≤4 μg/mL was highest in NA (95/91/88) > EU (85/81/77) > LA (78/71/69). Confirmed EC ESBL-producers varied from 1.2%/3.8%/6.3% in NA/EU/LA, respectively, and for KSP, 6.2%/14.3%/28.4%; all EC and >99% of KSP were inhibited by CARBs.

Conclusions: DOR combines the spectrum and potency of IPM against Gram-positives and of MEM against Gram-negatives. As multidrug resistance spreads, especially among Gram-negative BSI pathogens, there is a critical need for additional drugs to treat infections caused by these organisms.

a. Updated to correct errors in isolate totals.

INTRODUCTION

Bacteremia is associated with significant morbidity and mortality, requiring prompt assessment as to probable source followed by appropriate medical and/or surgical interventions. The increased complexity of patients requiring hospitalization, seriousness of their underlying condition(s), and the widespread use of indwelling devices have all created increased risks for bacteremia. Inadequate empiric antimicrobial therapy can be associated with adverse outcomes, including increased mortality, and antimicrobial resistance is an added complication known to result in treatment failures. Knowledge of the most likely causative organisms and their expected resistance patterns can increase the probability of selecting an effective antimicrobial for empiric therapy.

Doripenem is an investigational parenteral carbapenem currently under development by Johnson & Johnson and represents the first new antipseudomonal drug in advanced development in nearly a decade. It has the favorable characteristics of the carbapenem class, including stability to extended-spectrum β-lactamases (ESBLs) and AmpC cephalosporinases, resistance to inactivation by renal dehydropeptidases, and low potential for central nervous system toxicity. Earlier in vitro studies of this carbapenem have shown the compound to have a spectrum and potency versus Gram-positive cocci most similar to imipenem, and a Gram-negative activity most like meropenem (eg, 2- to 4-fold greater than imipenem).[1-4]

Resistance to licensed carbapenems has, however, increasingly been reported among *Pseudomonas aeruginosa* and *Acinetobacter* spp. strains in certain geographic regions (Europe, South America, Asia-Pacific) and may be produced by the expression of acquired metallo-β-lactamases or oxacillinases, or by a combination of AmpC hyper-production, outer membrane porin deletions, and/or up-regulated efflux mechanisms. Carbapenem resistance among Enterobacteriaceae, while very rare, has been documented both sporadically and in clonal outbreaks and may be due to a variety of plasmid-mediated Ambler class A serine carbapenemases, including KPC, NmcA, IMI, and SME.

The objective of the current study was to examine the susceptibility profiles and antibiograms of doripenem and comparator agents tested against contemporary bloodstream infection isolates as part of a longitudinal international surveillance protocol. A total of 29,176 isolates were tested by reference methods of the Clinical and Laboratory Standards Institute (CLSI; formerly NCCLS) using current CLSI interpretive criteria.[5,6]

MATERIALS AND METHODS

Bacterial Strain Collection

A total of 29,176 non-duplicate, consecutive clinical isolates were submitted from 59 to 64 medical centers located in North America, South America, and Europe as part of an international surveillance program during the years 2003 to 2005. Isolates originated from patients with documented bloodstream infections. The distribution of leading genera and species is presented in Table 1.

Table 1. Summary of In Vitro Activity of 3 Carbapenems Against Leading Gram-positive and Gram-negative Bloodstream Pathogens Collected as Part of a Global Surveillance Program (2003 to 2005)

	Doripenem		Meropenem		Imipenem	
Organism (no. tested)	**MIC_{90} (μg/mL)**	**% at Indicated MIC[a]**	**MIC_{90} (μg/mL)**	**% Susceptible**	**MIC_{90} (μg/mL)**	**% Susceptible**
S. aureus (oxacillin-susceptible; 4,652)	≤0.06	100	0.12	100	≤0.12	100
Coagulase-negative staphylococci (oxacillin-susceptible; 650)	≤0.06	100	0.12	100	≤0.12	100
S. pneumoniae (669)	0.25	90	0.5	88	–	–
β-Hemolytic streptococci (767)	≤0.06	100	≤0.06	100	≤0.12	100
E. coli (6,432)	≤0.06	100	≤0.06	100	≤0.5	100
Klebsiella spp. (2,729)	≤0.06	98	≤0.06	98	≤0.5	98
Enterobacter spp. (1,452)	0.12	>99	0.12	>99	1	>99
Serratia (544)	0.25	98	0.12	98	1	>99
P. aeruginosa (1,944)	8	87	>8	82	>8	79
Acinetobacter spp. (713)	>8	78	>8	74	>8	78

a. 0.25 μg/mL for *S. pneumoniae*, 0.5 μg/mL for β-hemolytic streptococci, and 4 μg/mL for all others (equivalent to peer agents).

Susceptibility Test Methods

All strains were tested by the CLSI broth microdilution method using validated commercially prepared panels (TREK Diagnostics, Cleveland, Ohio) in cation-adjusted Mueller-Hinton broth (with 5% lysed horse blood added for testing of streptococci) against a variety of antimicrobial agents representing the most common classes and examples of drugs used in the empiric or directed treatment of the indicated pathogen. Interpretation of MIC results was in accordance with published CLSI criteria (2006). Enterobacteriaceae with elevated MICs (≥2 μg/mL) for ceftazidime and/or ceftriaxone and/or aztreonam were considered as ESBL-producing phenotypes; confirmatory testing was performed using cefotaxime and ceftazidime alone and in combination with clavulanic acid. Quality control (QC) strains utilized included *Escherichia coli* ATCC 25922 and 35218, *P. aeruginosa* ATCC 27853, *Staphylococcus aureus* ATCC 29213, and *Streptococcus pneumoniae* ATCC 49619; all QC results were within CLSI-specified ranges.

RESULTS

- Ranking pathogens (top 11; 91.4% of total) recovered from bloodstream infections in this global study included: *S. aureus* (22.6%), *E. coli* (22.0%), *Klebsiella* spp. (9.3%), *Enterococcus* spp. (9.2%), *P. aeruginosa* (6.7%), coagulase-negative staphylococci (7.4%), *Enterobacter* spp. (5.0%), β-hemolytic streptococci (2.6%), *Acinetobacter* spp. (2.4%), *S. pneumoniae* (2.3%), and *Serratia* spp. (1.9%) (Table 1).
- At MIC values of 0.25 for *S. pneumoniae*, 0.5 for β-hemolytic streptococci, and 4 μg/mL for all others (equivalent to peer agents), doripenem inhibited >97% of the top 10 bloodstream pathogens within its spectrum of activity (excluding enterococci and methicillin [oxacillin]-resistant staphylococci).
- All carbapenems were highly active against leading pathogens producing bloodstream infections (exceptions noted above) with doripenem being ≥2-fold (MIC_{90}) more active than meropenem against *S. aureus*, coagulase-negative staphylococci, *S. pneumoniae*, and *P. aeruginosa*, and 4- to 8-fold more active than imipenem against *Enterobacter* and *Serratia* spp. (Tables 2 to 4).

Table 2. In Vitro Activity of Doripenem in Comparison With Selected Antimicrobial Agents Tested Against Bloodstream Isolates of Staphylococci (Oxacillin-susceptible) and Streptococci

	MIC (μg/mL)			% by Category[a]	
Organism (no. tested)/ Antimicrobial Agent	**50%**	**90%**	**Range**	**Susceptible**	**Resistant**
S. aureus (4,652)					
Doripenem	≤0.06	≤0.06	≤0.06-4	–	–
Meropenem	0.12	0.12	≤0.06->16	99.9	0.1
Imipenem	≤0.12	≤0.12	≤0.12-4	100.0	0.0
Ceftriaxone	4	4	≤0.25->32	99.3	0.2
Ceftazidime	8	8	≤1->16	90.2	0.9
Cefepime	2	4	≤0.12->16	99.4	0.3
Piperacillin/tazobactam	1	2	≤0.12->256	99.7	0.3
Levofloxacin	≤0.5	≤0.5	≤0.5->4	93.4	6.1
Linezolid	2	2	0.12-2	100.0	–
Vancomycin	1	1	≤0.12-4	>99.9	0.0
Coagulase-negative staphylococci (650)					
Doripenem	≤0.06	≤0.06	≤0.06-4	–	–
Meropenem	0.12	0.12	≤0.06-4	100.0	0.0
Imipenem	≤0.12	≤0.12	≤0.12->8	99.8	0.2
Ceftriaxone	2	4	≤0.25-32	98.5	0.0
Ceftazidime	4	8	≤1->16	95.4	0.8
Cefepime	0.5	2	≤0.12-8	100.0	0.0
Piperacillin/tazobactam	≤0.5	1	≤0.5-8	100.0	0.0
Levofloxacin	0.25	2	≤0.03->4	89.1	9.5
Linezolid	1	1	0.12-2	100.0	–
Vancomycin	1	2	≤0.12-4	100.0	0.0
S. pneumoniae (669)					
Doripenem	≤0.06	0.25	≤0.06-1	–	–
Meropenem	≤0.06	0.5	≤0.06-1	88.7	1.5
Imipenem	≤0.12	≤0.12	≤0.12-1	91.6	0.5
Penicillin	≤0.015	2	≤0.015-4	78.6	10.6
Ceftriaxone	≤0.25	1	≤0.25-4	98.2	0.1
Cefepime	≤0.12	1	≤0.12-2	97.0	0.0
Levofloxacin	1	1	≤0.03->4	99.6	0.4
Linezolid	1	1	0.12-2	100.0	–
Vancomycin	0.25	0.5	≤0.12-1	100.0	–
β-Hemolytic streptococci (767)					
Doripenem	≤0.06	≤0.06	≤0.06-0.25	–	–
Meropenem	≤0.06	≤0.06	≤0.06-0.5	100.0	0.0
Penicillin	≤0.015	0.06	≤0.015-1	99.7	–
Ceftriaxone	≤0.25	≤0.25	≤0.25-4	99.5	–
Cefepime	≤0.12	≤0.12	≤0.12-2	99.7	–
Levofloxacin	0.5	1	0.06->4	99.5	0.5
Linezolid	1	1	0.25-2	100.0	–
Vancomycin	0.5	0.5	≤0.12-1	100.0	–

a. Break point criteria are those of CLSI M100-S16 (2006); – = no break points established.

- Confirmed *E. coli* ESBL-producers varied from 1.2%/3.8%/6.3% in North America/Europe/Latin America, respectively, and for *Klebsiella* spp., 6.2%/14.3%/28.4%.
- Doripenem and meropenem were equally active against confirmed ESBL-producing *E. coli* (MIC_{50} and MIC_{90}, ≤0.06 μg/mL) and *Klebsiella* spp. (MIC_{50} and MIC_{90}, ≤0.06 and 0.12 μg/mL, respectively). Both agents were at least 4-fold more active (MIC_{90}) than either imipenem or ertapenem against these resistant subsets (data not shown).
- Non-ESBL isolates of *Klebsiella* spp. with elevated carbapenem MICs (≥8 μg/mL; 30 isolates, 1.1%) were all found to express KPC β-lactamases and originated primarily from medical centers along the eastern seaboard (New York City area) of the United States.
- Breadth of coverage of the carbapenems (% at ≤4 μg/mL) against *P. aeruginosa* isolates was highest in North America (doripenem, 95%; meropenem, 91%; imipenem, 88%), intermediate in Europe (85%, 81%, and 77%) and lowest in South America (78%, 71%, and 69%).
- Only amikacin (88.8% susceptible) and polymyxin B (99.9%) provided equivalent or greater coverage of *P. aeruginosa* (Table 4).

Table 3. In Vitro Activity of Doripenem in Comparison With Selected Antimicrobial Agents Tested Against Bloodstream Isolates of Enterobacteriaceae

	MIC (μg/mL)			% by Category[a]	
Organism (no. tested)/ Antimicrobial Agent	**50%**	**90%**	**Range**	**Susceptible**	**Resistant**
E. coli (6,432)					
Doripenem	≤0.06	≤0.06	≤0.06-4	–	–
Meropenem	≤0.06	≤0.06	≤0.06-4	100.0	0.0
Imipenem	≤0.5	≤0.5	≤0.5-2	100.0	0.0
Ertapenem	≤0.06	≤0.06	≤0.06-4	>99.9	0.0
Piperacillin/tazobactam	2	4	≤0.12->256	95.9	2.1
Ceftriaxone	≤0.25	≤0.25	≤0.25->32	95.4	3.7
Ceftazidime	≤1	≤1	≤1->16	96.4	2.2
Cefepime	≤0.12	0.25	≤0.12->16	97.3	2.2
Levofloxacin	≤0.5	>4	≤0.5->4	82.8	15.1
Gentamicin	≤2	≤2	≤2->8	91.9	7.3
Klebsiella spp. (2,729)					
Doripenem	≤0.06	≤0.06	≤0.06->16	–	–
Meropenem	≤0.06	≤0.06	≤0.06->16	98.6	1.0
Imipenem	≤0.5	≤0.5	≤0.5->8	98.6	1.0
Ertapenem	≤0.06	0.12	≤0.06->16	97.6	1.8
Piperacillin/tazobactam	2	>64	0.25->64	84.8	11.9
Ceftriaxone	≤0.25	>32	≤0.25->32	83.2	11.9
Ceftazidime	≤1	>16	≤1->16	84.6	12.6
Cefepime	≤0.12	16	≤0.12->16	89.7	7.6
Levofloxacin	≤0.5	>4	≤0.5->4	87.3	10.1
Gentamicin	≤2	>8	≤2->8	83.7	14.5
Enterobacter spp. (1,452)					
Doripenem	≤0.06	0.12	≤0.06->8	–	–
Meropenem	≤0.06	0.12	≤0.06->8	99.5	0.3
Imipenem	≤0.5	1	≤0.5->8	99.2	0.4
Ertapenem	≤0.06	1	≤0.06->16	97.4	1.3
Piperacillin/tazobactam	2	64	0.25->256	80.0	9.7
Ceftriaxone	≤0.25	>32	≤0.25->32	76.5	14.5
Ceftazidime	≤1	>16	≤1->16	74.8	21.2
Cefepime	≤0.12	4	≤0.12->16	94.5	3.9
Levofloxacin	≤0.5	4	≤0.5->4	89.4	8.7
Gentamicin	≤2	8	≤2->8	88.7	9.7
Serratia spp. (544)					
Doripenem	0.12	0.25	0.03->16	–	–
Meropenem	≤0.06	0.12	≤0.06->8	98.9	0.9
Imipenem	≤0.5	1	≤0.5->8	99.3	0.7
Ertapenem	≤0.06	0.12	≤0.06->16	98.9	1.1
Piperacillin/tazobactam	2	16	≤0.5->256	90.1	2.4
Ceftriaxone	≤0.25	8	≤0.25->32	91.3	3.3
Ceftazidime	≤1	2	≤1->16	95.0	2.4
Cefepime	≤0.12	0.5	≤0.12->16	97.1	2.2
Levofloxacin	≤0.5	1	≤0.5->4	95.6	2.4
Gentamicin	≤2	≤2	≤2->8	91.2	7.6

a. Break point criteria are those of CLSI M100-S16 (2006); – = no break points established.

- Polymyxin B (99.8% susceptible) and the carbapenems (74.1% to 78.4%) were the most active agents studied against *Acinetobacter* spp., whereas greatest resistance was noted with ceftazidime (53.9%), piperacillin/tazobactam (49.5%), levofloxacin (45.7%), and amikacin (44.2%) (Table 4).

Table 4. In Vitro Activity of Doripenem in Comparison With Selected Antimicrobial Agents Tested Against Bloodstream Isolates of Non-fermentative Gram-negative Bacilli

	MIC (μg/mL)			% by Category[a]	
Organism (no. tested)/ Antimicrobial Agent	**50%**	**90%**	**Range**	**Susceptible**	**Resistant**
P. aeruginosa (1,944)					
Doripenem	0.5	8	≤0.06->8	–	–
Meropenem	0.5	>8	≤0.06->8	82.5	12.3
Imipenem	1	>8	≤0.5->8	79.6	11.8
Piperacillin/tazobactam	8	>64	≤0.5->64	82.2	17.8
Ceftazidime	4	>16	≤1->16	75.3	19.9
Cefepime	4	>16	≤0.12->16	76.5	12.1
Levofloxacin	0.5	>4	≤0.03->4	69.0	27.0
Tobramycin	0.5	>16	≤0.12->16	78.7	20.3
Amikacin	≤4	32	≤4->32	88.8	8.7
Polymyxin B	0.5	1	0.25->4	99.9	0.1
Acinetobacter spp. (713)					
Doripenem	1	>8	≤0.06->8	–	–
Meropenem	1	>8	≤0.06->8	74.1	16.1
Imipenem	≤0.5	>8	≤0.5->8	78.4	18.4
Ampicillin/sulbactam	8	32	≤0.25->32	54.4	32.5
Piperacillin/tazobactam	64	>64	≤0.12->64	39.4	49.5
Ceftazidime	>16	>16	≤1->16	39.6	53.9
Cefepime	16	>16	≤0.12->16	46.4	39.6
Levofloxacin	4	>4	≤0.03->4	44.7	45.7
Tobramycin	1	>16	≤0.12->16	62.0	34.2
Amikacin	16	>32	≤0.25->32	52.2	44.2
Polymyxin B	≤0.5	≤0.5	≤0.5-4	99.8	0.2

a. Break point criteria are those of CLSI M100-S16 (2006); – = no break points established.

CONCLUSIONS

- Ranking pathogens producing bloodstream infections in this global study (91.4% of total) included: *S. aureus*, *E. coli*, *Klebsiella* spp., *Enterococcus* spp., *P. aeruginosa*, coagulase-negative staphylococci, *Enterobacter* spp., β-hemolytic streptococci, *Acinetobacter* spp., *S. pneumoniae*, and *Serratia* spp.
- Doripenem inhibited >97% of the top 10 bloodstream pathogens within its spectrum of activity (excluding enterococci and methicillin [oxacillin]-resistant staphylococci) at MICs of 0.25 μg/mL for *S. pneumoniae*, 0.5 μg/mL for β-hemolytic streptococci, and 4 μg/mL for all others (equivalent to peer agents).
- Enterobacteriaceae non-susceptible to carbapenems were almost all *Klebsiella* spp. expressing KPC β-lactamases.
- Among all *P. aeruginosa* tested as part of this international surveillance program, doripenem inhibited 87.3% at ≤4 μg/mL compared with 82.5% for meropenem and 79.6% for imipenem; only polymyxin B was found to inhibit nearly all (>99%) *P. aeruginosa* and *Acinetobacter* spp.
- As multidrug resistance spreads, especially among Gram-negative pathogens that cause blood infections, there is a critical need for additional drugs; with its broad-spectrum profile, doripenem should be considered for future development.

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