A-003

Antimicrobial Activity of Doripenem Tested Against Bloodstream Infection Isolates from North America (2003-2006)

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Abstract

Background: Patient comorbidities and widespread use of indwelling devices have increased rates of nosocomial bloodstream infections (BSI), requiring prompt management with targeted antimicrobials for favorable outcomes. We summarize the results of a North American (NA) surveillance program comparing doripenem (DOR), a broad-spectrum parenteral carbapenem (CARB) in advanced clinical development, with numerous other agents against contemporary BSI pathogens.

Methods: Nonduplicate consecutive BSI isolates (16,874) were collected from ≥24 medical centers each year in NA. Identifications were confirmed by the central monitor, and all isolates were susceptibility (S) tested using CLSI methods against DOR, meropenem (MEM), imipenem (IPM), and other comparators.

Results: DOR inhibited 98.7% of the top 11 ranked BSI pathogens, excluding oxacillin (OXA)-resistant (R) *S. aureus* (43.9%), coagulase-negative staphylococci (79.1%), and enterococci, at tested S breakpoints.

	MIC_{50}/% Inhibited[a]		
Ranking BSI Organisms (no. tested)	DOR	MEM	IPM
S. aureus (OXA-S; 2576)	≤0.06/100.0	0.12/100.0	≤0.12/100
E. coli (EC; 2965)	≤0.06/100.0	≤0.06/100.0	0.25/100.0
Klebsiella spp. (KSP; 1557)	≤0.06/97.7	≤0.06/97.2	0.5/97.2
Coagulase (-) staphylococci (OXA-S; 208)	≤0.06/100.0	0.12/100	≤0.12/100
P. aeruginosa (PSA; 834)	4/95.8	4/91.6	8/88.1
Enterobacter spp. (ESP; 807)	0.12/99.9	0.12/99.5	1/99.6
Beta-hemolytic streptococci (BHS; 651)	≤0.06/100.0	≤0.06/100.0	-
S. pneumoniae (SPN; 399)	0.25/99.7	0.25/90.4	≤0.12/90.9
Serratia (331)	0.25/98.8	≤0.06/98.8	1/99.4
Proteus mirabilis (PM; 270)	0.25/100.0	≤0.06/100.0	2/100.0
Acinetobacter spp. (ASP; 263)	8/88.2	8/86.3	4/90.9

a. CLSI breakpoints used for MEM and IPM; for DOR, ≤1 ug/mL for SPN and BHS, and ≤4 ug/mL for all other organisms.

All CARBs were highly active against the ranked pathogens, with DOR and MEM being equally active against SPN, BHS, EC, KSP, ESP, and ASP; DOR being ≥2-fold (MIC_{90}) more active than MEM against SA and CNS; and 4- to 8-fold more active than IPM against many Gram-negative bacilli. % PSA with DOR/MEM/IPM MIC values ≤4 mg/mL were 95.8/91.6/88.1. Confirmed ESBL-producers included EC (2.3%), KSP (8.0%), ESP (2.7%), and PM (1.5%); all were inhibited by ≤2 mg/mL of DOR. All ceftazidime-R ESP (19.7%; AmpC hyperproducers) were DOR-S. CARB non-S KSP (36 isolates) and ESP (1 isolate) were KPC carbapenemase-producing strains, originating from the eastern USA.

Conclusions: DOR, an investigational CARB, combines the spectrum and potency of IPM against Gram-positive and of MEM against Gram-negative organisms, including enhanced coverage against PSA. As multidrug-R spreads, especially among Gram-negative BSI pathogens, accelerated drug development becomes a critical need.

Introduction

- Given the significant morbidity and mortality associated with bacteremia, prompt assessment as to probable source followed by appropriate medical and/or surgical interventions are required. 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 empirical 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 under development by Johnson and Johnson that has the favorable characteristics of the carbapenem class, including stability to extended-spectrum ь-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, two- to fourfold greater than imipenem).
- Resistance to licensed carbapenems has 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-b-lactamases, oxacillinases, or by a combination of AmpC hyper-production, outer membrane porin deletions, and/or upregulated efflux mechanisms. Carbapenem resistance among Enterobacteriaceae, while 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.
- We examined the susceptibility profiles of doripenem and comparator agents tested against contemporary bloodstream infection isolates originating in North America as part of a longitudinal international surveillance protocol. A total of 16,874 isolates were tested by reference methods of the Clinical and Laboratory Standards Institute (CLSI; formerly NCCLS).

Materials and Methods

- Bacterial Strain Collection. A total of 16,874 nonduplicate, consecutive clinical isolates were submitted from 25 medical centers located in North America as part of an international surveillance program during the years 2003 to 2006. Isolates originated from patients with documented bloodstream infections. The distribution of leading genera and species is presented in Table 1.
- Susceptibility Test Methods. All strains were tested by the CLSI broth microdilution method using validated commercially prepared panels (TREK Diagnostics, Cleveland, OH) 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 (2007). Enterobacteriaceae (*Escherichia coli*, *Klebsiella* spp.) with elevated MIC values (≥2 mg/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 *E. 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 12; 93.8% of total) recovered from bloodstream infections in North America for 2003 to 2006 included: *S. aureus* (27.2%), *E. coli* (17.6%), *Enterococcus* spp. (12.9%), *Klebsiella* spp. (9.2%), coagulase-negative staphylococci (5.9%), *P. aeruginosa* (4.9%), *Enterobacter* spp. (4.8%), ь-haemolytic streptococci (3.8%), *S. pneumoniae* (2.4%), *Serratia* spp. (2.0%), *Proteus mirabilis* (1.6%), and *Acinetobacter* spp. (1.5%; Table 1).
- At MIC values of 1 for *S. pneumoniae* and ь-haemolytic streptococci and 4 mg/mL for all others (equivalent to peer agents), doripenem inhibited 99.0% of the top 11 bloodstream pathogens within its spectrum of activity (excludes enterococci and methicillin [oxacillin]-resistant staphylococci).
- All carbapenems were highly active against leading pathogens producing bloodstream infections (exceptions noted above) with doripenem being at least twofold (MIC_{50}) more active than meropenem against staphylococci; equivalent to meropenem against *S. pneumoniae*, *P. aeruginosa*, and *Acinetobacter* spp.; and four- to eightfold more active than imipenem against *Enterobacter* and *Serratia* spp. (Tables 2-4).
- Prevalence of *E. coli* and *Klebsiella* spp. displaying an ESBL-phenotype was 3.3% to 4.2% and 12.1% to 13.2%, respectively. Following confirmatory testing, ESBL rates were 2.3 and 8.0% for *E. coli* and *Klebsiella* spp.; no doripenem MIC exceeded 0.25 and 2 mg/mL, respectively, for these groups.
- Doripenem and meropenem were equally active against confirmed ESBL-producing *E. coli* and *Klebsiella* spp. (MIC_{50} and MIC_{90} values, ≤0.06 and 0.12 mg/mL) and both agents were twofold more active (MIC_{90}) than imipenem.
- Non-ESBL isolates of *Klebsiella* spp. with elevated carbapenem MIC values (≥8 mg/mL; 44 isolates, 2.8%) were mostly found to express KPC ь-lactamases and originated primarily from medical centers along the mid-Atlantic seaboard (New York City area) of the United States.
- Among carbapenems, doripenem provided the best coverage against *P. aeruginosa* (% inhibited at ≤4 mg/mL: doripenem, 95.8%; meropenem, 91.6%; imipenem, 88.1%).
- Only amikacin (97.8% susceptible) and polymyxin B (99.9%) provided greater coverage of *P. aeruginosa* (Table 4).
- Polymyxin B (99.6% susceptible) and the carbapenems (86.3 to 90.9%) were the most active agents studied against *Acinetobacter* spp., whereas greatest resistance was noted for ceftazidime (40.7%), levofloxacin (36.5%), cefepime (28.5%) and piperacillin/ tazobactam (27.0%)(Table 4).

Table 1. Summary of the In Vitro Activity of Three Carbapenems Against Leading Gram-Positive and Gram-Negative Bloodstream Pathogens Collected as Part of the Doripenem Surveillance Program (North America, 2003-2006)

	Doripenem		Meropenem		Imipenem	
Organism (no. tested)	MIC_{50} (mg/mL)	% at ≤ indicated MIC[a]	MIC_{50} (mg/mL)	% Susceptible[b]	MIC_{50} (mg/mL)	% Susceptible[b]
S. aureus (oxacillin-susceptible; 2576)	≤0.06	100.0	0.12	100.0	≤0.12	100.0
Coagulase-negative staphylococci (oxacillin-susceptible; 208)	≤0.06	100.0	0.12	100.0	≤0.12	100.0
S. pneumoniae (399)	0.25	99.7	0.25	90.4	≤0.12	90.9
ь-haemolytic streptococci (651)	≤0.06	100.0	≤0.06	100.0	-	-
E. coli (2965)	≤0.06	100.0	≤0.06	100.0	0.25	100.0
Klebsiella spp. (1557)	≤0.06	97.7	≤0.06	97.2	≤0.5	97.2
Enterobacter spp. (807)	0.12	99.9	≤0.12	99.5	1	99.6
Serratia (331)	0.25	98.8	≤0.06	98.8	1	99.4
P. aeruginosa (834)	4	95.8	4	91.6	8	88.1
P. mirabilis (270)	0.25	100.0	≤0.06	100.0	2	100.0
Acinetobacter spp. (263)	8	88.2	8	86.3	4	90.9

a. ≤1 mg/mL for *S. pneumoniae* and ь-haemolytic streptococci and ≤4 mg/mL for all others (equivalent to peer agents).
b. Breakpoints those of CLSI M100-S17 [2007].

Table 2. In Vitro Activity of Doripenem in Comparison to Selected Antimicrobial Agents Tested Against Bloodstream Isolates of Staphylococci (Oxacillin-Susceptible) and Streptococci Originating From North America

	MIC (mg/mL)			% by Category[a]	
Organism (no. tested)/antimicrobial agent	50%	90%	Range	Susceptible	Resistant
S. aureus (oxacillin-susceptible; 2576)					
Doripenem	≤0.06	≤0.06	≤0.06-2	-	-
Meropenem	0.12	0.12	≤0.06-1	100.0	0.0
Imipenem	≤0.12	≤0.12	≤0.12-4	100.0	0.0
Ceftriaxone	4	4	≤0.25-32	99.5	0.0
Ceftazidime	8	8	≤1->16	92.0	0.3
Cefepime	2	4	0.25-8	100.0	0.0
Piperacillin-tazobactam	1	2	≤0.5-64	99.8	0.2
Levofloxacin	≤0.25	0.5	≤0.25->4	91.6	7.7
Linezolid	2	2	0.12-2	100.0	-
Vancomycin	1	1	0.25-2	>99.9	0.0
Coagulase-negative staphylococci (oxacillin-susceptible; 208)					
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	≤0.12-1	100.0	0.0
Ceftriaxone	2	4	≤0.25-16	97.6	0.0
Ceftazidime	4	8	≤1->16	93.8	1.4
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	>4	≤0.03->4	77.4	20.7
Linezolid	1	1	≤0.06-2	100.0	-
Vancomycin	1	2	0.25-4	100.0	0.0
S. pneumoniae (399)					
Doripenem	≤0.06	0.25	≤0.06-2	-	-
Meropenem	≤0.06	0.25	≤0.06-1	90.4	2.9
Imipenem	≤0.12	≤0.12	≤0.12-1	90.9	1.0
Penicillin	≤0.015	1	≤0.015-8	74.2	9.5
Ceftriaxone	≤0.25	0.5	≤0.25-8	98.7	0.5
Cefepime	≤0.12	0.5	≤0.12-4	98.0	0.3
Levofloxacin	1	1	0.06->4	99.7	0.3
Linezolid	1	1	0.12-2	100.0	-
Vancomycin	0.25	0.5	≤0.12-1	100.0	-
ь-haemolytic streptococci (651)					
Doripenem	≤0.06	≤0.06	≤0.06-0.5	-	-
Meropenem	≤0.06	≤0.06	≤0.06-0.25	100.0	0.0
Penicillin	0.03	0.06	≤0.015-0.25	99.8	-
Ceftriaxone	≤0.25	≤0.25	≤0.25-1	99.7	-
Cefepime	≤0.12	≤0.12	≤0.12-1	99.8	-
Levofloxacin	0.5	1	≤0.06->4	99.1	0.9
Linezolid	1	1	≤0.06-2	100.0	-
Vancomycin	0.5	0.5	≤0.12-1	100.0	-

a. Breakpoint criteria are those of CLSI M100-S17 [2007]. - = no breakpoints established.

Table 3. In Vitro Activity of Doripenem in Comparison to Selected Antimicrobial Agents Tested Against Bloodstream Isolates of Enterobacteriaceae Originating From North America

	MIC (mg/mL)			% by Category[a]	
Organism (no. tested)/antimicrobial agent	50%	90%	Range	Susceptible	Resistant
E. coli (2965)					
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	≤0.5-4	100.0	0.0
Ertapenem	≤0.06	≤0.06	≤0.06-8	>99.9	<0.1
Piperacillin-tazobactam	2	4	≤0.5->256	97.1	1.7
Ceftriaxone	≤0.25	≤0.25	≤0.25->32	97.6	1.6 (3.3)[b]
Ceftazidime	≤1	≤1	≤1->16	97.6	1.7 (4.2)[b]
Cefepime	≤0.12	≤0.12	≤0.12->16	99.0	0.9
Levofloxacin	≤0.5	>4	≤0.5->4	84.6	14.4
Gentamicin	≤2	≤2	≤2->8	92.3	7.1
Klebsiella spp. (1557)					
Doripenem	≤0.06	≤0.06	≤0.06->16	-	-
Meropenem	≤0.06	≤0.06	≤0.06->16	97.2	2.5
Imipenem	≤0.5	≤0.5	≤0.5->8	97.2	2.4
Ertapenem	≤0.06	≤0.06	≤0.06->16	96.7	3.1
Piperacillin-tazobactam	2	32	≤0.5->256	89.3	8.5
Ceftriaxone	≤0.25	8	≤0.25->32	91.0	5.6 (13.2)[b]
Ceftazidime	≤1	16	≤1->16	89.8	9.3 (12.1)[b]
Cefepime	≤0.12	1	≤0.12->16	95.1	3.5
Levofloxacin	≤0.5	4	≤0.5->4	88.4	9.8
Gentamicin	≤2	≤2	≤2->8	92.7	5.9
Enterobacter spp. (807)					
Doripenem	≤0.06	0.12	≤0.06->8	-	-
Meropenem	≤0.06	0.12	≤0.06->8	99.5	<0.1
Imipenem	≤0.5	1	≤0.5->8	99.6	<0.1
Ertapenem	≤0.06	0.5	≤0.06->16	98.4	0.9
Piperacillin-tazobactam	2	64	≤0.5->256	84.5	6.3
Ceftriaxone	≤0.25	>32	≤0.25->32	82.3	10.3
Ceftazidime	≤1	>16	≤1->16	80.2	16.5
Cefepime	≤0.12	2	≤0.12->16	97.6	1.6
Levofloxacin	≤0.5	≤0.5	≤0.5->4	93.4	4.6
Gentamicin	≤2	≤2	≤2->8	91.9	6.9
Serratia spp. (331)					
Doripenem	0.12	0.25	≤0.06->16	-	-
Meropenem	≤0.06	≤0.06	≤0.06->8	98.8	1.2
Imipenem	≤0.5	1	≤0.5->8	99.4	0.6
Ertapenem	≤0.06	≤0.06	≤0.06->16	98.8	1.2
Piperacillin-tazobactam	2	4	≤0.5->256	97.0	0.6
Ceftriaxone	≤0.25	2	≤0.25->32	95.8	0.6
Ceftazidime	≤1	≤1	≤1->16	96.1	2.7
Cefepime	≤0.12	0.5	≤0.12->16	99.1	0.9
Levofloxacin	≤0.5	1	≤0.5->4	97.9	0.9
Gentamicin	≤2	≤2	≤2->8	95.2	2.7

a. Breakpoint criteria are those of CLSI M100-S17 [2007]. - = no breakpoints established.
b. Numbers in parentheses represent the percentage of isolates meeting the ESBL-phenotype criteria of CLSI (2007).

Table 4. In Vitro Activity of Doripenem in Comparison to Selected Antimicrobial Agents Tested Against Bloodstream Isolates of Non-Fermentative Gram-Negative Bacilli Originating From North America

	MIC (mg/mL)			% by Category[a]	
Organism (no. tested)/antimicrobial agent	50%	90%	Range	Susceptible	Resistant
P. aeruginosa (834)					
Doripenem	0.5	4	≤0.06->8	-	-
Meropenem	0.5	4	≤0.06->8	91.6	4.4
Imipenem	1	8	≤0.5->8	88.1	5.2
Piperacillin-tazobactam	4	64	≤0.5->64	90.8	9.2
Ceftazidime	2	16	≤1->16	86.8	9.2
Cefepime	2	16	≤0.12->16	87.9	5.4
Levofloxacin	≤0.5	>4	≤0.5->4	70.0	23.0
Tobramycin	0.5	1	≤0.25->16	93.0	6.4
Amikacin	≤4	8	≤4->32	97.8	1.6
Polymyxin B	≤1	≤1	≤1->4	99.9	0.1
Acinetobacter spp. (263)					
Doripenem	0.5	8	≤0.06->8	-	-
Meropenem	0.5	8	≤0.06->8	86.3	9.5
Imipenem	≤0.5	4	≤0.5->8	90.9	4.9
Ampicillin-sulbactam	4	>16	≤2->16	72.6	18.6
Piperacillin-tazobactam	16	>64	≤0.5->64	57.4	27.0
Ceftazidime	8	>16	≤1->16	53.2	40.7
Cefepime	8	>16	≤0.12->16	55.5	28.5
Levofloxacin	≤0.5	>4	≤0.5->4	58.6	36.5
Tobramycin	0.5	>16	≤0.25->16	77.2	19.8
Amikacin	≤4	>32	≤4->32	81.7	13.7
Polymyxin B	≤1	≤1	≤1->4	99.6	0.4

a. Breakpoint criteria are those of CLSI M100-S17 [2007]. - = no breakpoints established.

Conclusions

- Ranking pathogens producing bloodstream infections in North America (93.8% of total) included: *S. aureus*, *E. coli*, *Enterococcus* spp., *Klebsiella* spp., coagulase-negative staphylococci, *P. aeruginosa*, *Enterobacter* spp., ь-haemolytic streptococci, *S. pneumoniae*, *Serratia* spp., *P. mirabilis*, and *Acinetobacter* spp.
- Doripenem, an investigational carbapenem, inhibited 99.0% of the top 11 bloodstream pathogens within its spectrum of activity (excluding enterococci and oxacillin-resistant staphylococci) at MIC values of 1 mg/mL for *S. pneumoniae* and ь-haemolytic streptococci, and 4 mg/mL for all others (equivalent to peer agents).
- Enterobacteriaceae nonsusceptible to carbapenems were dominated by *Klebsiella* spp. expressing KPC serine ь-lactamases.
- Among tested North American *P. aeruginosa*, doripenem inhibited 95.8% at ≤4 mg/mL compared with 91.6% for meropenem and 88.1% for imipenem; only polymyxin B was observed to inhibit nearly all (>99%) *P. aeruginosa* and *Acinetobacter* spp.
- There is a critical need for new agents as multidrug resistance emerges, especially among Gram-negative bloodstream pathogens. If approved, doripenem may represent a new choice for broad-spectrum therapeutic coverage.

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