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Spectrum and Activity of Doripenem, an Investigational Carbapenem, Tested Against Bacterial Pathogens Recovered From Patients Hospitalized With Pneumonia (Europe: 2004-2006)

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ABSTRACT

Objectives: To summarize the activity of doripenem, an investigational broad-spectrum parenteral carbapenem in late-stage clinical development, against leading bacterial pathogens recovered from European patients with hospital-acquired pneumonia. Emerging resistance among hospital-acquired pneumonia pathogens, especially gram-negative bacilli, compromises patient management and contributes to excess morbidity and mortality.

Methods: A total of 2127 consecutive, non-duplicate isolates determined as the cause of pneumonia in hospitalized patients were submitted from 24 medical centers in Europe (2004-2006). The hospital-acquired pneumonia pathogens that were included are summarized in Table 1. Susceptibility testing of doripenem and comparator agents was performed using current CLSI methods and interpretive criteria, including those for characterization of ESBL phenotypes.

Results: Results for doripenem are in Table 1. Ranking of the top 8 occurring hospital-acquired pneumonia isolates and key resistance characteristics were: *Pseudomonas aeruginosa* (21.5% meropenem-non-susceptible) > *Staphylococcus aureus* (441 isolates; 39.7% oxacillin-resistant) > *Escherichia coli* (11.2% ESBL) > *Klebsiella* spp. (31.4% ESBL) > *Enterobacter* spp. (31.5% ceftazidime-resistant) > *Acinetobacter* spp. (66% meropenem-non-susceptible) > *Serratia* spp. > *Stenotrophomonas maltophilia* (68 isolates; not shown). Oxacillin-resistant *S. aureus* and *S. maltophilia* are inherently resistant to carbapenems and are not discussed further. Overall, doripenem inhibited 90.8% of the 7 top-ranked pathogens within its spectrum of activity at ≤4 mg/L (equivalent to breakpoints of peer carbapenems) compared with 88.6% for meropenem and 86.3% for imipenem. Elevated doripenem, meropenem, and imipenem MIC values were detected among *P. aeruginosa* ($MIC_{50/90}$ values: 0.5/8; 1/>8; 1/>8 mg/L; respectively) and *Acinetobacter* spp. ($MIC_{50/90}$ values: 8/>8; 4/>8; 8/>8 mg/L). Strains of metallo-β-lactamase-producing *P. aeruginosa* (IMP, VIM series) were detected in Italy, Greece, and Turkey.

Table 1. Hospital-Acquired Pneumonia Isolates and Potency Characteristics for Doripenem

	Doripenem MIC (mg/L)			
Organism (no. tested)	**50%**	**90%**	**Range**	**% ≤2/≤4**
P. aeruginosa (488)	0.5	8	≤0.6->8	72/85
S. aureus (oxacillin-susceptible; 266)	≤0.06	≤0.06	≤0.06-0.5	100/100
E. coli (241)	≤0.06	≤0.06	≤0.06-0.25	100/100
Klebsiella spp. (229)	≤0.06	≤0.06	≤0.06->8	>99/100
Enterobacter spp. (146)	≤0.06	0.12	≤0.06-1	100/100
Acinetobacter spp. (134)	8	>8	≤0.06->8	38/46
Serratia spp. (75)	0.12	0.25	≤0.06-0.5	100/100

Conclusion: The described prevalences of resistant phenotypes among contemporary European hospital-acquired pneumonia pathogens increasingly complicates therapeutic management decisions. Doripenem is a promising carbapenem that may represent an important choice among broad-spectrum agents for this indication (hospital-acquired pneumonia), especially given its enhanced activity against ESBLs and *P. aeruginosa*.

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INTRODUCTION

Nosocomial respiratory tract infections are significant causes of morbidity and mortality, and have become much more difficult to manage with the escalating resistances being seen among all usual pathogen groups, including *Staphylococcus aureus*, Enterobacteriaceae, and non-fermentative gram-negative bacilli. The decrease in utility of many penicillins, cephalosporins, β-lactamase inhibitor combinations, aminoglycosides, and fluoroquinolones, among other classes of antimicrobics, has created a critical need for new agents.

As an antimicrobial class, carbapenems are innately stable to most β-lactamases of Ambler classes 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 is a potent parenteral carbapenem in late-stage clinical trials and is known to have a spectrum and potency versus gram-positive cocci most similar to imipenem, and gram-negative activity most similar to meropenem (e.g., 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 anti-pseudomonal 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 contemporary (2004-2006) European collection of leading bacterial agents recovered from patients hospitalized with pneumonia.

MATERIALS AND METHODS

Bacterial Strain Collection

A total of 2127 non-duplicate, consecutive clinical isolates recovered from hospitalized patients with documented pneumonia were submitted from 24 medical centers located in Europe as part of a larger international surveillance program (2004-2006). The distribution of ranking species and strains included *P. aeruginosa* (488), *S. aureus* (441 isolates), *Escherichia coli* (241), *Klebsiella* spp. (229), *Enterobacter* spp. (146), *Acinetobacter* spp. (134), and *Serratia* spp. (75).

Susceptibility Test Methods

All strains were tested by the Clinical and Laboratory Standards Institute (CLSI [2006]) broth microdilution method using validated, commercially prepared panels (TREK Diagnostics, Ohio, USA) in cation-adjusted Mueller-Hinton broth 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 CLSI published criteria; breakpoints for doripenem have not been established. Quality control strains utilized included *E. coli* ATCC 25922 and 35218, *P. aeruginosa* ATCC 27853, and *S. aureus* ATCC 29213. All quality control results were within CLSI-specified ranges (2007).

RESULTS

- Prevalence of ranking hospital pneumonia pathogens recovered during 2004-2006 from European patients included: *P. aeruginosa* (22.9%) > *S. aureus* (20.7%) > *E. coli* (11.3%) > *Klebsiella* spp. (10.8%) > *Enterobacter* spp. (6.9%) > *Acinetobacter* spp. (6.3%) > *Serratia* spp. (3.5%) > *Stenotrophomonas maltophilia* (3.2%); others (14.4%) (Table 2)

Table 2. Summary of the In Vitro Activity of 3 Carbapenems Against Leading Gram-Positive and -Negative Pathogens Producing Hospital-Acquired Pneumonia Collected as Part of a European Surveillance Program (2004-2006)

	MIC (mg/L)		Cumulative Percentage Inhibited at MIC (mg/L)			
Organism (number tested)	**50%**	**90%**	**≤1**	**2**	**4***	**8**
P. aeruginosa (488)						
Doripenem	0.5	8	62.1	71.9	85.0	92.6
Meropenem	1	>8	59.4	67.2	78.5	89.1
Imipenem	1	>8	53.1	64.1	69.5	83.6
S. aureus (oxacillin-susceptible; 266)						
Doripenem	≤0.06	≤0.06	100.0			
Meropenem	0.12	0.12	100.0			
Imipenem	≤0.12	≤0.12	100.0			
E. coli (241)						
Doripenem	≤0.06	≤0.06	100.0			
Meropenem	≤0.06	≤0.06	100.0			
Imipenem	≤0.12	0.25	100.0			
Klebsiella spp. (229)						
Doripenem	≤0.06	≤0.06	99.1	99.6	100.0	
Meropenem	≤0.06	≤0.06	99.1	100.0		
Imipenem	≤0.12	0.5	97.8	99.1	99.6	100
Enterobacter spp. (146)						
Doripenem	≤0.06	0.12	98.6	100.0		
Meropenem	≤0.06	0.12	98.6	100.0		
Imipenem	0.5	1	92.5	97.3	99.3	100.0
Acinetobacter spp. (134)						
Doripenem	8	>8	32.1	38.1	46.3	63.4
Meropenem	8	>8	29.9	37.3	44.0	57.5
Imipenem	4	>8	33.6	44.8	51.5	55.2
Serratia spp. (75)						
Doripenem	0.12	0.25	100.0			
Meropenem	≤0.06	≤0.06	100.0			
Imipenem	0.5	1	100.0			

*CLSI-susceptible breakpoint for meropenem and imipenem at ≤4 mg/L.

- Key resistance characteristics included: meropenem-nonsusceptible *P. aeruginosa* (21.5%) and *Acinetobacter* spp. (56.0%); oxacillin-resistant *S. aureus* (39.7%); fluoroquinolone-resistant *E. coli* (17.8%); ESBL screen-positive *E. coli* (10.0%-10.4%) and *Klebsiella* spp. (28.8%-31.4%); ceftazidime-resistant *Enterobacter* spp. (31.5%; Table 3). Oxacillin-resistant *S. aureus* and *S. maltophilia* are inherently resistant to all carbapenems
- Overall, doripenem inhibited 90.8% of the 7 top-ranked pathogens within its spectrum of activity at ≤4 mg/L (equivalent to breakpoints of peer carbapenems) compared with 86.3% for imipenem and 88.6% for meropenem
- Elevated MIC values for doripenem, meropenem, and imipenem were detected among *P. aeruginosa* ($MIC_{50/90}$ values: 0.5/8; 1/>8; 1/>8 mg/L; respectively). Doripenem inhibited a greater percentage of isolates at ≤4 mg/L (85.0%) than did meropenem (78.5%) or imipenem (69.5%)
- *Acinetobacter* spp. displayed high resistance rates to all tested agents; only polymyxin B was uniformly active against this species (97.8% susceptible; Table 3)

Table 3. In Vitro Activity of Doripenem in Comparison to Selected Antimicrobial Agents Tested Against the 7 Most Prevalent Isolates Producing Hospital-Acquired Pneumonia Collected as Part of a European Surveillance Program (2004-2006)

	MIC (mg/L)			Percentage by Category*	
Organism (no. tested)/ antimicrobial agent	**50%**	**90%**	**Range**	**Susceptible**	**Resistant**
P. aeruginosa (488)					
Doripenem	0.5	8	≤0.06->8	-	-
Meropenem	1	>8	≤0.06->8	78.5	10.9
Imipenem	1	>8	≤0.12->8	69.5	16.4
Piperacillin-tazobactam	8	>64	≤0.5->64	80.1	19.9
Ceftazidime	4	>16	≤1->16	73.8	19.1
Cefepime	4	>16	≤0.12->16	75.6	10.5
Levofloxacin	1	>4	0.06->4	65.2	28.7
Gentamicin	≤2	>8	≤2->8	72.7	25.3
Polymyxin B	1	1	≤0.5->4	99.8	0.2
S. aureus (oxacillin-susceptible; 266)					
Doripenem	≤0.06	≤0.06	≤0.06-025	-	-
Meropenem	0.12	0.12	≤0.06-0.25	100.0	0.0
Imipenem	≤0.12	≤0.12	≤0.12	100.0	0.0
Ceftriaxone	4	4	1-16	99.6	0.0
Ceftazidime	8	8	4->16	94.7	0.4
Cefepime	2	4	1-8	100.0	0.0
Piperacillin-tazobactam	1	2	≤0.5-8	100.0	0.0
Levofloxacin	≤0.5	1	≤0.5->4	90.2	9.4
Gentamicin	≤2	≤2	≤2->8	98.9	1.1
Linezolid	2	2	0.12-2	100.0	-
Vancomycin	1	1	0.5-2	100.0	0.0
E. coli (241)					
Doripenem	≤0.06	≤0.06	≤0.06-0.5	-	-
Meropenem	0.12	0.12	≤0.06-0.5	100.0	0.0
Imipenem	≤0.12	≤0.12	≤0.12-1	100.0	0.0
Ertapenem	≤0.06	≤0.06	≤0.06-4	99.6	0.0
Piperacillin-tazobactam	2	32	≤0.5->64	88.0	6.6
Ceftriaxone	≤0.25	4	≤0.25->32	90.5	7.5 (10.4)†
Ceftazidime	≤1	≤1	≤1->16	92.9	3.7 (10.0)†
Cefepime	≤0.12	1	≤0.12->16	95.0	4.1
Levofloxacin	≤0.5	>4	≤0.5->4	78.4	17.8
Gentamicin	≤2	≤2	≤2->8	92.5	7.1
Klebsiella spp. (229)					
Doripenem	≤0.06	≤0.06	≤0.06-4	-	-
Meropenem	≤0.06	≤0.06	≤0.06-2	100.0	0.0
Imipenem	≤0.12	0.5	≤0.12-8	99.6	0.0
Ertapenem	≤0.06	0.12	≤0.06-2	100.0	0.0
Piperacillin-tazobactam	4	>64	≤0.5->64	79.5	16.2
Ceftriaxone	≤0.25	>32	≤0.25->32	76.0	17.0 (31.4)†
Ceftazidime	≤1	>16	≤1->16	79.5	17.5 (28.8)†
Cefepime	≤0.12	16	≤0.12->16	87.3	9.2
Levofloxacin	≤0.5	>4	≤0.5->4	83.8	12.2
Gentamicin	≤2	>8	≤2->8	82.5	17.0
Enterobacter spp. (146)					
Doripenem	≤0.06	0.12	≤0.06-2	-	-
Meropenem	≤0.06	0.12	≤0.06-2	100.0	0.0
Imipenem	0.5	1	≤0.12-8	99.3	0.0
Ertapenem	≤0.06	1	≤0.06->8	98.6	1.4
Piperacillin-tazobactam	4	>64	≤0.5->64	67.8	12.3
Ceftriaxone	1	>32	≤0.25->32	65.8	18.5
Ceftazidime	≤1	>16	≤1->16	59.6	31.5
Cefepime	≤0.12	4	≤0.12->16	96.6	2.1
Levofloxacin	≤0.5	>4	≤0.5->4	82.2	17.8
Gentamicin	≤2	8	≤2->8	89.7	6.8
Acinetobacter spp. (134)					
Doripenem	8	>8	≤0.06->8	-	-
Meropenem	8	>8	≤0.06->8	44.0	42.5
Imipenem	4	>8	≤0.12->8	51.5	44.8
Ampicillin-sulbactam	16	>16	≤2->32	36.6	47.8
Piperacillin-tazobactam	>64	>64	≤0.5->64	20.9	69.4
Ceftazidime	>16	>16	≤1->16	24.6	69.4
Cefepime	16	>16	≤0.12->16	31.3	47.0
Levofloxacin	>4	>4	≤0.5->4	21.6	68.7
Gentamicin	>8	>8	≤2->8	25.4	72.4
Polymyxin B	≤0.5	≤0.5	≤0.5->4	97.8	2.2
Serratia spp. (75)					
Doripenem	0.12	0.25	≤0.06-0.25	-	-
Meropenem	≤0.06	≤0.06	≤0.06-0.12	100.0	0.0
Imipenem	0.5	1	0.25-1	100.0	0.0
Ertapenem	≤0.06	≤0.06	≤0.06-0.5	100.0	0.0
Piperacillin-tazobactam	2	32	≤0.5->64	88.0	5.3
Ceftriaxone	≤0.25	8	≤0.25->32	93.3	2.7
Ceftazidime	≤1	≤1	≤1->16	97.3	1.3
Cefepime	≤0.12	0.5	≤0.12->16	98.7	1.3
Levofloxacin	≤0.5	1	≤0.5->4	96.0	1.3
Gentamicin	≤2	8	≤2->8	88.0	8.0

*Breakpoint criteria are those of CLSI M100-S17 (2007); - = no breakpoints established.
†Percentage meeting CLSI criteria for an ESBL phenotype (≥2 mg/L).

- Strains of metallo-β-lactamase-producing *P. aeruginosa* were detected in Italy (IMP), Greece (VIM), and Turkey (VIM)

CONCLUSIONS

- Pathogens producing >85% of hospital-acquired pneumonia in European patients for 2004 to 2006 included *P. aeruginosa* (22.9%), *S. aureus* (20.7%), *E. coli* (11.3%), *Klebsiella* spp. (10.8%), *Enterobacter* spp. (6.9%), *Acinetobacter* spp. (6.3%), *Serratia* spp. (3.5%), and *S. maltophilia* (3.2%)
- Doripenem was broadly active against this collection, inhibiting 90.8% of the 7 top-ranked pathogens within its spectrum of activity at a concentration of ≤4 mg/L, the equivalent breakpoint of peer agents
- Among tested *P. aeruginosa* isolates, doripenem inhibited 85.0% at ≤4 mg/L compared with 78.5% for meropenem and 68.5% for imipenem
- Doripenem, an investigational carbapenem, appears as a promising agent for treatment of hospital-acquired pneumonia targeting those pathogens in European patients expressing the most rapidly increasing (and problematic) resistant phenotypes

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