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In Vitro Antimicrobial Activity of Doripenem, a New Carbapenem

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The doripenem MICs at which 90% of the tested strains were inhibited ranged from 0.03 to 1 μg/ml for 10 species of *Enterobacteriaceae* ($n = 351$), from 0.03 to 0.12 μg/ml for oxacillin-susceptible staphylococci ($n = 119$), from 4 to 32 μg/ml for oxacillin-resistant staphylococci ($n = 64$), from ≤0.008 to 0.06 μg/ml for penicillin-susceptible streptococci ($n = 132$), and from 1 to 4 μg/ml for penicillin-resistant streptococci ($n = 51$). Overall, doripenem demonstrated in vitro activity similar to that of meropenem against gram-negative pathogens and to that of imipenem against gram-positive pathogens.

The synthesis of new carbapenems remains an area of intense research because of the broad-spectrum antibacterial activity of this chemical class (6–9, 11, 12). Doripenem (formerly S-4661) is an investigational parenteral 1β-methlycarbapenem, originally discovered by Shionogi & Co., Ltd. (Osaka, Japan) (1), that is currently being developed in the United States by Peninsula Pharmaceuticals, Inc. (Alameda, Calif.) for the treatment of hospitalized patients with serious systemic bacterial infections. Preliminary reports indicate that doripenem has activity against a broad spectrum of bacterial pathogens (6, 9, 11; R. N. Jones, H. Huynh, and D. J. Biedenbach, Abstr. 43rd Intersci. Conf. Antimicrob. Agents Chemother., abstr. F-527, 2003), that it has favorable pharmacokinetic properties (K. Shiba, M. Nakashima, H. Tanimura, H. Okada, J. Shimada, Abstr. 37th Intersci. Conf. Antimicrob. Agents Chemother., abstr. F-217, 1997; D. A. Thye, T. Kilfoil, A. Leighton, and M. Wikler, Abstr. 43rd Intersci. Conf. Antimicrob. Agents Chemother., abstr. A-21, 2003), that it is safe and well tolerated in humans (D. A. Thye et al., 43rd ICAAC), that it is not hydrolyzed by renal dehydropeptidase I like imipenem (2), and that it does not promote the release of endotoxin (10). The objectives of the present study were to investigate the in vitro activity of doripenem against a collection of clinically relevant gram-negative and gram-positive pathogens and to compare the activity of doripenem with the activities of other carbapenems, broad-spectrum cephalosporins, and piperacillin-tazobactam.

(Part of this research was presented at the 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Ill., 14 to 17 September 2003.)

Isolates tested in the present study were selected from the isolate repository maintained by Focus Technologies (Herndon, Va.) based upon the isolates' species or group identity and their antimicrobial susceptibility testing phenotype; isolates were chosen irrespective of the age of the patient (<1 to 98 years), the specimen source (respiratory, wound, urine, or blood) from which they were isolated, or any other patient demographic parameter. All isolates tested in the present study were collected in U.S. clinical microbiology laboratories from 1999 to 2003. In total, 815 isolates were tested, of which 381 were gram-negative isolates and 434 were gram-positive isolates. Each isolate was taken from frozen stock (−70°C) and subcultured twice onto sheep blood agar; the identity of each isolate was confirmed by using standard clinical laboratory methods applicable to each species or organism group (3).

Antimicrobial susceptibility testing was performed in accordance with the recommended procedures of the National Committee for Clinical Laboratory Standards (NCCLS) (4) by using frozen broth microdilution panels prepared by TREK Diagnostics (Cleveland, Ohio). All isolates were tested against cefepime, ceftriaxone, doripenem, ertapenem, imipenem, meropenem, and piperacillin-tazobactam. Additional antimicrobial agents were tested to confirm antimicrobial susceptibility testing phenotypes and for reference. These agents varied with bacterial species or organism group as follows: gram-negative bacteria were also tested against ampicillin, amoxicillin-clavulanate, aztreonam, ceftazidime, and ciprofloxacin; staphylococci and enterococci were also tested against oxacillin, levofloxacin, and vancomycin; and streptococci were also tested against penicillin, azithromycin, and levofloxacin. Isolates were defined as susceptible, intermediate, or resistant to antimicrobial agents according to NCCLS standard M100-S13 (5). Extended-spectrum β-lactamase (ESBL) confirmatory testing was performed by using the NCCLS recommended method for isolates of *Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca* (5).

The doripenem MICs at which 90% of the strains were inhibited (MIC_{90}) ranged from 0.03 to 0.5 μg/ml for all *Enterobacteriaceae* tested, with the exception of *Proteus mirabilis* (MIC_{90}, 1 μg/ml) (Table 1). The MICs of doripenem for the isolates of *Enterobacteriaceae* tested were similar to the MICs of ertapenem and meropenem, while imipenem MICs were approximately 2 to 4 doubling dilutions higher than the MICs of the other three carbapenems (Fig. 1). The MICs at which 50% of the strains were inhibited, MIC_{90}s, modal MICs, and MIC ranges of doripenem for ESBL-negative and ESBL-positive *E. coli* and *K. pneumoniae* were similar; the MICs of doripenem for ceftazidime-intermediate and -resistant isolates of other *Enterobacteriaceae* were identical or 1 to 2 doubling

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TABLE 1. In vitro MICs of doripenem and comparative β-lactams for *A. baumannii*, 10 species of *Enterobacteriaeae*, enterococci, staphylococci, and streptococci[a]

Organism, antimicrobial agent, and isolate phenotype	No. of isolates tested	MIC (μg/ml)			
		Range	Mode	MIC_{50}	MIC_{90}
Acinetobacter baumannii					
Aztreonam					
Ceftazidime-susceptible	20	8–>32	16	32	>32
Ceftazidime-intermediate or resistant	10	16–>32	>32	>32	>32
Cefepime					
Ceftazidime-susceptible	20	≤0.5–16	4	4	8
Ceftazidime-intermediate or resistant	10	8–>32	>32	>32	>32
Ceftriaxone					
Ceftazidime-susceptible	20	4–32	16	16	32
Ceftazidime-intermediate or resistant	10	32–>64	>64	>64	>64
Doripenem					
Ceftazidime-susceptible	20	0.12–1	0.12	0.25	1
Ceftazidime-intermediate or resistant	10	0.25–>16	1	1	>16
Ertapenem					
Ceftazidime-susceptible	20	0.5–16	2	2	8
Ceftazidime-intermediate or resistant	10	2–>16	8	8	>16
Imipenem					
Ceftazidime-susceptible	20	0.06–0.5	0.25	0.25	0.25
Ceftazidime-intermediate or resistant	10	0.25–>16	1	1	8
Meropenem					
Ceftazidime-susceptible	20	0.12–2	0.25	0.25	1
Ceftazidime-intermediate or resistant	10	0.25–>16	2	2	16
Piperacillin-tazobactam					
Ceftazidime-susceptible	20	≤1–32	≤1	4	32
Ceftazidime-intermediate or resistant	10	32–>128	>128	128	>128
Citrobacter freundii					
Aztreonam					
Ceftazidime-susceptible	21	≤1–8	≤1	≤1	≤1
Ceftazidime-intermediate or resistant	20	4–>32	16	16	>32
Cefepime					
Ceftazidime-susceptible	21	≤0.5	≤0.5	≤0.5	≤0.5
Ceftazidime-intermediate or resistant	20	≤0.5–16	≤0.5	1	4
Ceftriaxone					
Ceftazidime-susceptible	21	≤0.5–2	≤0.5	≤0.5	≤0.5
Ceftazidime-intermediate or resistant	20	8–>64	32	32	>64
Doripenem					
Ceftazidime-susceptible	21	≤0.015–0.06	0.03	0.03	0.03
Ceftazidime-intermediate or resistant	20	0.03–0.25	0.06	0.06	0.12
Ertapenem					
Ceftazidime-susceptible	21	≤0.015–0.03	≤0.015	≤0.015	≤0.015
Ceftazidime-intermediate or resistant	20	0.03–0.5	0.12	0.12	0.5
Imipenem					
Ceftazidime-susceptible	21	0.12–1	1	1	1
Ceftazidime-intermediate or resistant	20	0.5–2	0.5	0.5	1
Meropenem					
Ceftazidime-susceptible	21	≤0.015–0.03	≤0.015	≤0.015	0.03
Ceftazidime-intermediate or resistant	20	≤0.015–0.12	0.06	0.06	0.06
Piperacillin-tazobactam					
Ceftazidime-susceptible	21	≤1–8	≤1	≤1	4
Ceftazidime-intermediate or resistant	20	4–>128	128	64	>128

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TABLE 1—*Continued*

Organism, antimicrobial agent, and isolate phenotype	No. of isolates tested	MIC (μg/ml)			
		Range	Mode	MIC_{50}	MIC_{90}
Enterobacter aerogenes					
Aztreonam					
Ceftazidime-susceptible	23	≤1–8	≤1	≤1	2
Ceftazidime-intermediate or resistant	20	8–>32	16	16	>32
Cefepime					
Ceftazidime-susceptible	23	≤0.5–1	≤0.5	≤0.5	≤0.5
Ceftazidime-intermediate or resistant	20	≤0.5–>32	≤0.5	≤0.5	4
Ceftriaxone					
Ceftazidime-susceptible	23	≤0.5–4	≤0.5	≤0.5	1
Ceftazidime-intermediate or resistant	20	4–>64	32	32	>64
Doripenem					
Ceftazidime-susceptible	23	0.03–0.12	0.06	0.06	0.12
Ceftazidime-intermediate or resistant	20	0.06–0.12	0.12	0.12	0.12
Ertapenem					
Ceftazidime-susceptible	23	≤0.015–0.25	≤0.015	≤0.015	0.06
Ceftazidime-intermediate or resistant	20	0.06–1	0.12	0.25	0.5
Imipenem					
Ceftazidime-susceptible	23	0.5–2	2	2	2
Ceftazidime-intermediate or resistant	20	0.5–2	0.5	0.5	1
Meropenem					
Ceftazidime-susceptible	23	≤0.015–0.06	0.03	0.03	0.06
Ceftazidime-intermediate or resistant	20	0.03–0.12	0.06	0.06	0.12
Piperacillin-tazobactam					
Ceftazidime-susceptible	23	≤1–32	2	2	4
Ceftazidime-intermediate or resistant	20	16–>128	64	64	>128
Enterobacter cloacae					
Aztreonam					
Ceftazidime-susceptible	23	≤1–8	≤1	≤1	2
Ceftazidime-intermediate or resistant	19	16–>32	>32	>32	>32
Cefepime					
Ceftazidime-susceptible	23	≤0.5	≤0.5	≤0.5	≤0.5
Ceftazidime-intermediate or resistant	19	≤0.5–16	1	2	8
Ceftriaxone					
Ceftazidime-susceptible	23	≤0.5–4	≤0.5	≤0.5	1
Ceftazidime-intermediate or resistant	19	16–>64	>64	>64	>64
Doripenem					
Ceftazidime-susceptible	23	0.03–0.12	0.03	0.03	0.06
Ceftazidime-intermediate or resistant	19	0.06–0.25	0.12	0.12	0.25
Ertapenem					
Ceftazidime-susceptible	23	≤0.015–0.5	≤0.015	≤0.015	0.06
Ceftazidime-intermediate or resistant	19	0.06–1	0.5	0.5	1
Imipenem					
Ceftazidime-susceptible	23	0.06–4	0.5	0.5	2
Ceftazidime-intermediate or resistant	19	0.5–2	0.5	0.5	1
Meropenem					
Ceftazidime-susceptible	23	≤0.015–0.25	0.03	0.03	0.06
Ceftazidime-intermediate or resistant	19	0.06–0.25	0.06	0.06	0.25
Piperacillin-tazobactam					
Ceftazidime-susceptible	23	≤1–16	2	2	8
Ceftazidime-intermediate or resistant	19	8–>128	128	128	>128
Escherichia coli					
Aztreonam					
ESBL-negative	22	≤1–8	≤1	≤1	≤1
ESBL-positive	18	4–>32	>32	>32	>32

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TABLE 1—*Continued*

Organism, antimicrobial agent, and isolate phenotype	No. of isolates tested	MIC (μg/ml)			
		Range	Mode	MIC_{50}	MIC_{90}
Cefepime					
ESBL-negative	22	≤0.5–>32	≤0.5	≤0.5	≤0.5
ESBL-positive	18	≤0.5–>32	>32	32	>32
Ceftriaxone					
ESBL-negative	22	≤0.5–>64	≤0.5	≤0.5	≤0.5
ESBL-positive	18	1–>64	>64	>64	>64
Doripenem					
ESBL-negative	22	≤0.015–0.06	0.03	0.03	0.03
ESBL-positive	18	≤0.015–0.06	0.03	0.03	0.06
Ertapenem					
ESBL-negative	22	≤0.015–0.06	≤0.015	≤0.015	≤0.015
ESBL-positive	18	≤0.015–1	0.03	0.03	0.5
Imipenem					
ESBL-negative	22	0.06–0.5	0.12	0.12	0.5
ESBL-positive	18	0.12–0.5	0.25	0.25	0.5
Meropenem					
ESBL-negative	22	≤0.015–0.03	≤0.015	≤0.015	≤0.015
ESBL-positive	18	≤0.015–0.12	≤0.015	≤0.015	0.06
Piperacillin-tazobactam					
ESBL-negative	22	≤1–16	2	2	4
ESBL-positive	18	2–>128	4	16	>128
Klebsiella oxytoca					
Aztreonam					
ESBL-negative	20	≤1–>32	≤1	≤1	≤1
Cefepime					
ESBL-negative	20	≤0.5–8	≤0.5	≤0.5	≤0.5
Ceftriaxone					
ESBL-negative	20	≤0.5–>64	≤0.5	≤0.5	≤0.5
Doripenem					
ESBL-negative	20	0.03–0.12	0.03	0.03	0.06
Ertapenem					
ESBL-negative	20	≤0.015–0.25	≤0.015	≤0.015	≤0.015
Imipenem					
ESBL-negative	20	0.12–0.5	0.25	0.25	0.5
Meropenem					
ESBL-negative	20	≤0.015–0.12	0.03	0.03	0.03
Piperacillin-tazobactam					
ESBL-negative	20	≤1–>128	≤1	2	4
Klebsiella pneumoniae					
Aztreonam					
ESBL-negative	20	≤1–2	≤1	≤1	≤1
ESBL-positive	20	4–>32	>32	>32	>32
Cefepime					
ESBL-negative	20	≤0.5	≤0.5	≤0.5	≤0.5
ESBL-positive	20	≤0.5–>32	>32	8	>32
Ceftriaxone					
ESBL-negative	20	≤0.5	≤0.5	≤0.5	≤0.5
ESBL-positive	20	≤0.5–>64	>64	64	>64
Doripenem					
ESBL-negative	20	0.03–0.25	0.03	0.03	0.12
ESBL-positive	20	≤0.015–0.25	0.06	0.06	0.12

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TABLE 1—*Continued*

Organism, antimicrobial agent, and isolate phenotype	No. of isolates tested	MIC (μg/ml)			
		Range	Mode	MIC_{50}	MIC_{90}
Ertapenem					
ESBL-negative	20	≤0.015–0.25	≤0.015	≤0.015	≤0.015
ESBL-positive	20	≤0.015–0.5	0.12	0.06	0.25
Imipenem					
ESBL-negative	20	0.12–1	0.25	0.25	1
ESBL-positive	20	0.06–1	0.5	0.5	1
Meropenem					
ESBL-negative	20	≤0.015–0.25	0.03	0.03	0.03
ESBL-positive	20	≤0.015–0.12	0.06	0.03	0.06
Piperacillin-tazobactam					
ESBL-negative	20	≤1–8	2	2	4
ESBL-positive	20	4–>128	>128	>128	>128
Morganella morganii					
Aztreonam					
Ceftazidime-susceptible	20	≤1	≤1	≤1	≤1
Ceftazidime-intermediate or resistant	1	2			
Cefepime					
Ceftazidime-susceptible	20	≤0.5–1	≤0.5	≤0.5	≤0.5
Ceftazidime-intermediate or resistant	1	≤0.5			
Ceftriaxone					
Ceftazidime-susceptible	20	≤0.5	≤0.5	≤0.5	≤0.5
Ceftazidime-intermediate or resistant	1	≤0.5			
Doripenem					
Ceftazidime-susceptible	20	0.06–0.5	0.25	0.25	0.5
Ceftazidime-intermediate or resistant	1	0.5			
Ertapenem					
Ceftazidime-susceptible	20	≤0.015–0.06	≤0.015	≤0.015	0.03
Ceftazidime-intermediate or resistant	1	0.06			
Imipenem					
Ceftazidime-susceptible	20	0.5–4	4	4	4
Ceftazidime-intermediate or resistant	1	4			
Meropenem					
Ceftazidime-susceptible	20	0.03–0.25	0.12	0.06	0.12
Ceftazidime-intermediate or resistant	1	0.12			
Piperacillin-tazobactam					
Ceftazidime-susceptible	20	≤1–4	≤1	≤1	≤1
Ceftazidime-intermediate or resistant	1	32			
Proteus mirabilis					
Aztreonam					
Ceftazidime-susceptible	22	≤1–>32	≤1	≤1	≤1
Ceftazidime-intermediate or resistant	19	≤1–>32	>32	>32	>32
Cefepime					
Ceftazidime-susceptible	22	≤0.5	≤0.5	≤0.5	≤0.5
Ceftazidime-intermediate or resistant	19	≤0.5–>32	>32	>32	>32
Ceftriaxone					
Ceftazidime-susceptible	22	≤0.5	≤0.5	≤0.5	≤0.5
Ceftazidime-intermediate or resistant	19	≤0.5–>64	≤0.5	8	64
Doripenem					
Ceftazidime-susceptible	22	0.12–2	0.25	0.5	1
Ceftazidime-intermediate or resistant	19	0.25–2	1	1	2
Ertapenem					
Ceftazidime-susceptible	22	≤0.015–0.25	≤0.015	≤0.015	0.06
Ceftazidime-intermediate or resistant	19	≤0.015–0.5	0.06	0.06	0.5

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TABLE 1—*Continued*

Organism, antimicrobial agent, and isolate phenotype	No. of isolates tested	MIC (μg/ml)			
		Range	Mode	MIC_{50}	MIC_{90}
Imipenem					
Ceftazidime-susceptible	22	1–4	4	4	4
Ceftazidime-intermediate or resistant	19	4–8	4	4	8
Meropenem					
Ceftazidime-susceptible	22	0.03–0.25	0.06	0.06	0.25
Ceftazidime-intermediate or resistant	19	0.06–0.25	0.12	0.12	0.25
Piperacillin-tazobactam					
Ceftazidime-susceptible	22	≤1–2	≤1	≤1	≤1
Ceftazidime-intermediate or resistant	19	≤1–4	≤1	≤1	2
Providencia spp.					
Aztreonam					
Ceftazidime-susceptible	20	≤1–2	≤1	≤1	≤1
Ceftazidime-intermediate or resistant	3	≤1–16			
Cefepime					
Ceftazidime-susceptible	20	≤0.5–2	≤0.5	≤0.5	≤0.5
Ceftazidime-intermediate or resistant	3	≤0.5–2			
Ceftriaxone					
Ceftazidime-susceptible	20	≤0.5–2	≤0.5	≤0.5	≤0.5
Ceftazidime-intermediate or resistant	3	≤0.5–8			
Doripenem					
Ceftazidime-susceptible	20	0.12–0.5	0.25	0.25	0.5
Ceftazidime-intermediate or resistant	3	0.25			
Ertapenem					
Ceftazidime-susceptible	20	≤0.015–0.12	≤0.015	≤0.015	0.06
Ceftazidime-intermediate or resistant	3	≤0.015–0.03			
Imipenem					
Ceftazidime-susceptible	20	0.5–4	2	2	2
Ceftazidime-intermediate or resistant	3	1–4			
Meropenem					
Ceftazidime-susceptible	20	0.03–0.12	0.06	0.06	0.12
Ceftazidime-intermediate or resistant	3	0.06–0.12			
Piperacillin-tazobactam					
Ceftazidime-susceptible	20	≤1–16	≤1	≤1	4
Ceftazidime-intermediate or resistant	3	2–8			
Serratia marcescens					
Aztreonam					
Ceftazidime-susceptible	21	≤1–>32	≤1	≤1	≤1
Ceftazidime-intermediate or resistant	19	2–>32	>32	>32	>32
Cefepime					
Ceftazidime-susceptible	21	≤0.5–2	≤0.5	≤0.5	≤0.5
Ceftazidime-intermediate or resistant	19	1–>32	32	8	>32
Ceftriaxone					
Ceftazidime-susceptible	21	≤0.5–64	≤0.5	≤0.5	2
Ceftazidime-intermediate or resistant	19	4–>64	>64	>64	>64
Doripenem					
Ceftazidime-susceptible	21	0.06–0.5	0.12	0.12	0.25
Ceftazidime-intermediate or resistant	19	0.12–0.25	0.12	0.12	0.25
Ertapenem					
Ceftazidime-susceptible	21	≤0.015–0.25	≤0.015	0.03	0.12
Ceftazidime-intermediate or resistant	19	≤0.015–0.5	0.12	0.12	0.5
Imipenem					
Ceftazidime-susceptible	21	0.25–4	1	1	2
Ceftazidime-intermediate or resistant	19	0.5–4	1	1	2

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TABLE 1—*Continued*

Organism, antimicrobial agent, and isolate phenotype	No. of isolates tested	MIC (μg/ml)			
		Range	Mode	MIC_{50}	MIC_{90}
Meropenem					
Ceftazidime-susceptible	21	0.03–0.12	0.06	0.06	0.06
Ceftazidime-intermediate or resistant	19	0.03–0.12	0.06	0.06	0.12
Piperacillin-tazobactam					
Ceftazidime-susceptible	21	≤1–16	2	2	4
Ceftazidime-intermediate or resistant	19	4–>128	>128	16	>128
Enterococcus faecalis					
Cefepime					
Vancomycin-susceptible	11	32–>32	>32	>32	>32
Vancomycin-intermediate	2	>32			
Vancomycin-resistant	7	32–>32			
Ceftriaxone					
Vancomycin-susceptible	11	>64	>64	>64	>64
Vancomycin-intermediate	2	>64			
Vancomycin-resistant	7	>64			
Doripenem					
Vancomycin-susceptible	11	1–8	8	4	8
Vancomycin-intermediate	2	4			
Vancomycin-resistant	7	2–8			
Ertapenem					
Vancomycin-susceptible	11	4–32	8	8	16
Vancomycin-intermediate	2	8–16			
Vancomycin-resistant	7	4–32			
Imipenem					
Vancomycin-susceptible	11	1–2	1	1	2
Vancomycin-intermediate	2	1–2			
Vancomycin-resistant	7	1–4			
Meropenem					
Vancomycin-susceptible	11	2–32	8	8	16
Vancomycin-intermediate	2	8			
Vancomycin-resistant	7	2–16			
Piperacillin-tazobactam					
Vancomycin-susceptible	11	2–4	4	4	4
Vancomycin-intermediate	2	2			
Vancomycin-resistant	7	≤1–4			
Enterococcus faecium					
Cefepime					
Vancomycin-susceptible	10	>32	>32	>32	>32
Vancomycin-resistant	11	>32	>32	>32	>32
Ceftriaxone					
Vancomycin-susceptible	10	16–>64	>64	>64	>64
Vancomycin-resistant	11	>64	>64	>64	>64
Doripenem					
Vancomycin-susceptible	10	2–>32	>32	32	>32
Vancomycin-resistant	11	>32	>32	>32	>32
Ertapenem					
Vancomycin-susceptible	10	16–>32	>32	>32	>32
Vancomycin-resistant	11	>32	>32	>32	>32
Imipenem					
Vancomycin-susceptible	10	2–>32	>32	16	>32
Vancomycin-resistant	11	>32	>32	>32	>32
Meropenem					
Vancomycin-susceptible	10	4–>32	>32	>32	>32
Vancomycin-resistant	11	>32	>32	>32	>32
Piperacillin-tazobactam					
Vancomycin-susceptible	10	4–>64	>64	>64	>64
Vancomycin-resistant	11	64–>64	>64	>64	>64

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TABLE 1—*Continued*

Organism, antimicrobial agent, and isolate phenotype	No. of isolates tested	MIC (μg/ml)			
		Range	Mode	MIC_{50}	MIC_{90}
Staphylococcus aureus					
Cefepime					
Oxacillin-susceptible	42	2–4	2	2	4
Oxacillin-resistant	23	8–>32	>32	>32	>32
Ceftriaxone					
Oxacillin-susceptible	42	≤1–4	2	2	4
Oxacillin-resistant	23	16–>64	>64	>64	>64
Doripenem					
Oxacillin-susceptible	42	≤0.015–0.06	0.03	0.03	0.06
Oxacillin-resistant	23	0.25–>32	32	4	32
Ertapenem					
Oxacillin-susceptible	42	0.06–0.25	0.12	0.12	0.25
Oxacillin-resistant	23	0.5–>32	>32	8	>32
Imipenem					
Oxacillin-susceptible	42	≤0.015–0.03	0.03	≤0.015	0.03
Oxacillin-resistant	23	0.06–>32	>32	1	>32
Meropenem					
Oxacillin-susceptible	42	0.03–0.25	0.06	0.06	0.12
Oxacillin-resistant	23	0.5–>32	>32	4	>32
Piperacillin-tazobactam					
Oxacillin-susceptible	42	≤1–2	≤1	≤1	2
Oxacillin-resistant	23	4–>64	>64	32	>64
Staphylococcus epidermidis					
Cefepime					
Oxacillin-susceptible	39	≤1	≤1	≤1	≤1
Oxacillin-resistant	17	≤1–16	4	4	16
Ceftriaxone					
Oxacillin-susceptible	39	≤1–2	≤1	≤1	2
Oxacillin-resistant	17	2–32	4	4	32
Doripenem					
Oxacillin-susceptible	39	≤0.015–0.06	0.03	0.03	0.03
Oxacillin-resistant	17	≤0.015–4	0.5	1	4
Ertapenem					
Oxacillin-susceptible	39	0.12–0.5	0.25	0.25	0.25
Oxacillin-resistant	17	0.25–32	2	2	16
Imipenem					
Oxacillin-susceptible	39	≤0.015	≤0.015	≤0.015	≤0.015
Oxacillin-resistant	17	0.03–4	0.06	0.12	2
Meropenem					
Oxacillin-susceptible	39	0.03–0.12	0.06	0.06	0.06
Oxacillin-resistant	17	0.06–16	1	1	8
Piperacillin-tazobactam					
Oxacillin-susceptible	39	≤1	≤1	≤1	≤1
Oxacillin-resistant	17	≤1–4	≤1	≤1	4
Coagulase-negative staphylococci (non-*S. epidermidis*)					
Cefepime					
Oxacillin-susceptible	38	≤1–4	≤1	≤1	2
Oxacillin-resistant	24	≤1–>32	2	4	>32
Ceftriaxone					
Oxacillin-susceptible	38	≤1–16	≤1	2	4
Oxacillin-resistant	24	2–>64	2	8	>64
Doripenem					
Oxacillin-susceptible	38	≤0.015–0.5	0.03	0.03	0.12
Oxacillin-resistant	24	0.03–32	0.06	0.5	16

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TABLE 1—*Continued*

Organism, antimicrobial agent, and isolate phenotype	No. of isolates tested	MIC (μg/ml)			
		Range	Mode	MIC_{50}	MIC_{90}
Ertapenem					
Oxacillin-susceptible	38	0.06–2	0.25	0.25	0.5
Oxacillin-resistant	24	0.12–>32	>32	2	>32
Imipenem					
Oxacillin-susceptible	38	≤0.015–0.06	≤0.015	≤0.015	0.03
Oxacillin-resistant	24	≤0.015–32	0.03	0.06	8
Meropenem					
Oxacillin-susceptible	38	≤0.015–1	0.06	0.06	0.25
Oxacillin-resistant	24	0.06–>32	0.5	1	32
Piperacillin-tazobactam					
Oxacillin-susceptible	38	≤1–2	≤1	≤1	≤1
Oxacillin-resistant	24	≤1–>64	≤1	2	64
Streptococcus pyogenes					
Penicillin					
Macrolide-susceptible	10	≤0.06	≤0.06	≤0.06	≤0.06
Cefepime					
Macrolide-susceptible	10	≤0.06	≤0.06	≤0.06	≤0.06
Ceftriaxone					
Macrolide-susceptible	10	≤0.03	≤0.03	≤0.03	≤0.03
Doripenem					
Macrolide-susceptible	10	≤0.008	≤0.008	≤0.008	≤0.008
Ertapenem					
Macrolide-susceptible	10	≤0.008–0.015	≤0.008	≤0.008	≤0.008
Imipenem					
Macrolide-susceptible	10	≤0.008	≤0.008	≤0.008	≤0.008
Meropenem					
Macrolide-susceptible	10	≤0.008	≤0.008	≤0.008	≤0.008
Piperacillin-tazobactam					
Macrolide-susceptible	10	≤0.06	≤0.06	≤0.06	≤0.06
Streptococcus agalactiae					
Penicillin					
Macrolide-susceptible	20	≤0.06	≤0.06	≤0.06	≤0.06
Macrolide-resistant	20	≤0.06	≤0.06	≤0.06	≤0.06
Cefepime					
Macrolide-susceptible	20	≤0.06–0.12	≤0.06	≤0.06	≤0.06
Macrolide-resistant	20	≤0.06–0.12	≤0.06	≤0.06	0.12
Ceftriaxone					
Macrolide-susceptible	20	≤0.03–0.06	0.06	0.06	0.06
Macrolide-resistant	20	≤0.03–0.12	0.06	0.06	0.06
Doripenem					
Macrolide-susceptible	20	≤0.008–0.015	0.015	0.015	0.015
Macrolide-resistant	20	0.015–0.03	0.015	0.015	0.015
Ertapenem					
Macrolide-susceptible	20	0.03–0.06	0.03	0.03	0.06
Macrolide-resistant	20	0.03–0.06	0.06	0.06	0.06
Imipenem					
Macrolide-susceptible	20	≤0.008–0.015	0.015	0.015	0.015
Macrolide-resistant	20	≤0.008–0.03	0.015	0.015	0.015
Meropenem					
Macrolide-susceptible	20	0.03	0.03	0.03	0.03
Macrolide-resistant	20	0.03–0.06	0.03	0.03	0.06
Piperacillin-tazobactam					
Macrolide-susceptible	20	0.25–0.5	0.25	0.25	0.25
Macrolide-resistant	20	0.25–0.5	0.25	0.25	0.5

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TABLE 1—*Continued*

Organism, antimicrobial agent, and isolate phenotype	No. of isolates tested	MIC (μg/ml)			
		Range	Mode	MIC_{50}	MIC_{90}
Streptococcus pneumoniae					
Cefepime					
Penicillin-susceptible	44	≤0.06	≤0.06	≤0.06	≤0.06
Penicillin-intermediate	23	≤0.06–1	0.5	0.25	1
Penicillin-resistant	33	0.5–4	1	1	2
Ceftriaxone					
Penicillin-susceptible	44	≤0.03	≤0.03	≤0.03	≤0.03
Penicillin-intermediate	23	≤0.03–0.5	0.5	0.25	0.5
Penicillin-resistant	33	0.5–8	1	1	4
Doripenem					
Penicillin-susceptible	44	≤0.008–0.015	≤0.008	≤0.008	≤0.008
Penicillin-intermediate	23	0.015–0.5	0.25	0.12	0.25
Penicillin-resistant	33	0.25–1	1	0.5	1
Ertapenem					
Penicillin-susceptible	44	≤0.008–0.03	0.015	0.015	0.015
Penicillin-intermediate	23	0.03–1	0.03	0.25	1
Penicillin-resistant	33	0.5–4	0.5	1	2
Imipenem					
Penicillin-susceptible	44	≤0.008–0.015	≤0.008	≤0.008	≤0.008
Penicillin-intermediate	23	≤0.008–0.25	0.12	0.06	0.12
Penicillin-resistant	33	0.12–1	0.5	0.5	1
Meropenem					
Penicillin-susceptible	44	≤0.008–0.03	≤0.008	≤0.008	≤0.008
Penicillin-intermediate	23	0.015–0.5	0.25	0.12	0.5
Penicillin-resistant	33	0.25–2	0.5	0.5	1
Piperacillin-tazobactam					
Penicillin-susceptible	44	≤0.06–0.12	≤0.06	≤0.06	≤0.06
Penicillin-intermediate	23	≤0.06–4	2	1	4
Penicillin-resistant	33	2–>8	4	4	8
Viridans group streptococci					
Cefepime					
Penicillin-susceptible	38	≤0.06–0.5	≤0.06	0.12	0.5
Penicillin-intermediate	4	0.25–1			
Penicillin-resistant	18	0.5–>4	2	2	>4
Ceftriaxone					
Penicillin-susceptible	38	≤0.03–0.5	0.06	0.06	0.25
Penicillin-intermediate	4	0.25–1			
Penicillin-resistant	18	1–>8	4	4	4
Doripenem					
Penicillin-susceptible	38	≤0.008–0.06	0.03	0.03	0.06
Penicillin-intermediate	4	0.03–1			
Penicillin-resistant	18	0.25–4	1	1	4
Ertapenem					
Penicillin-susceptible	38	0.03–0.5	0.06	0.06	0.25
Penicillin-intermediate	4	0.12–2			
Penicillin-resistant	18	1–>8	4	4	8
Imipenem					
Penicillin-susceptible	38	≤0.008–0.06	0.015	0.015	0.06
Penicillin-intermediate	4	0.03–1			
Penicillin-resistant	18	0.12–4	2	2	2
Meropenem					
Penicillin-susceptible	38	≤0.008–0.12	0.03	0.03	0.06
Penicillin-intermediate	4	0.06–1			
Penicillin-resistant	18	0.25–4	2	2	4
Piperacillin-tazobactam					
Penicillin-susceptible	38	≤0.06–2	0.12	0.12	1
Penicillin-intermediate	4	0.25–8			
Penicillin-resistant	18	0.5–>8	>8	8	>8

[a] MIC_{50}, the MIC at which 50% of the isolates are inhibited by an antimicrobial agent. The mode, MIC_{50}, and MIC_{90} were not calculated for phenotype groups of <10 isolates.

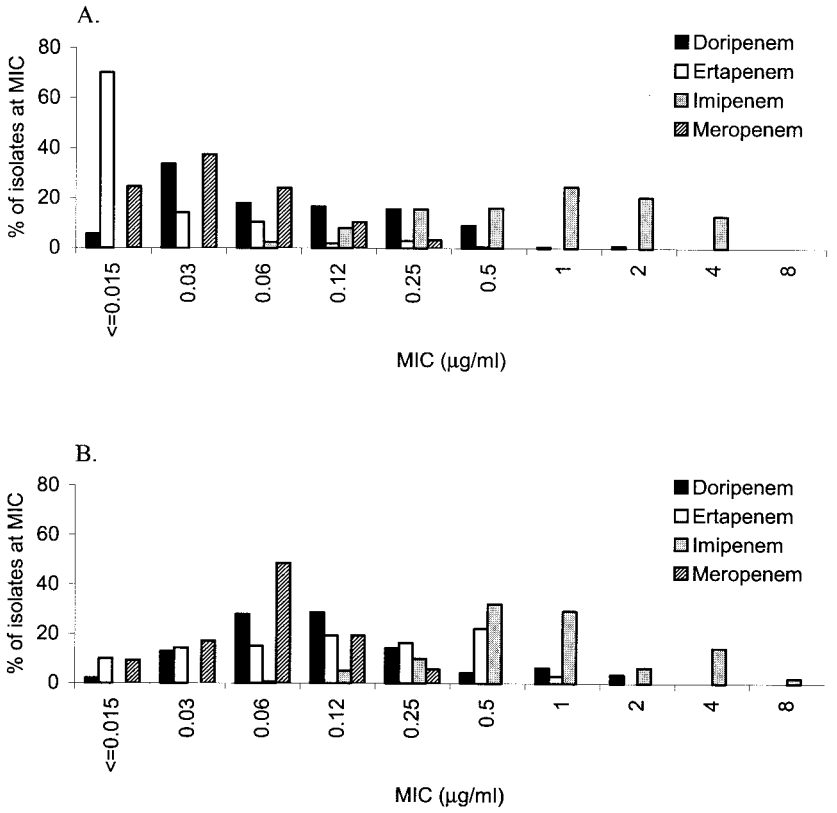

FIG. 1. MIC distributions of doripenem, ertapenem, imipenem, and meropenem against 211 isolates of ESBL-negative or ceftazidime-susceptible *Enterobacteriaceae* (A) and 140 isolates of ESBL-positive or ceftazidime-intermediate or ceftazidime-resistant *Enterobacteriaceae* (B).

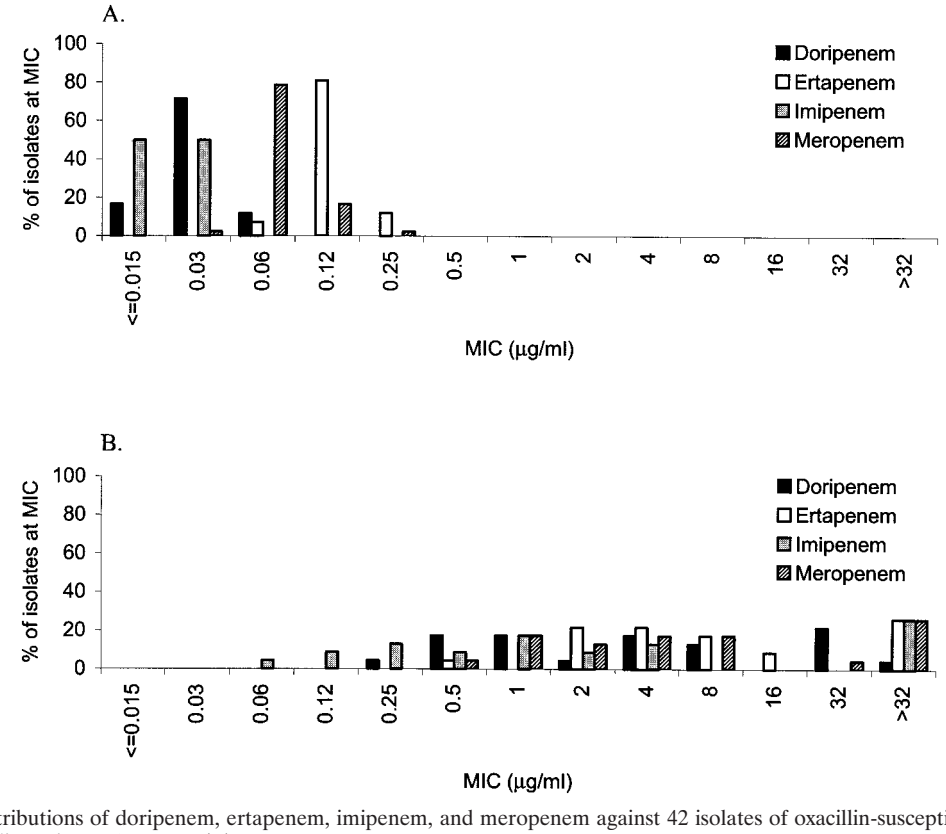

FIG. 2. MIC distributions of doripenem, ertapenem, imipenem, and meropenem against 42 isolates of oxacillin-susceptible *S. aureus* (A) and 23 isolates of oxacillin-resistant *S. aureus* (B).

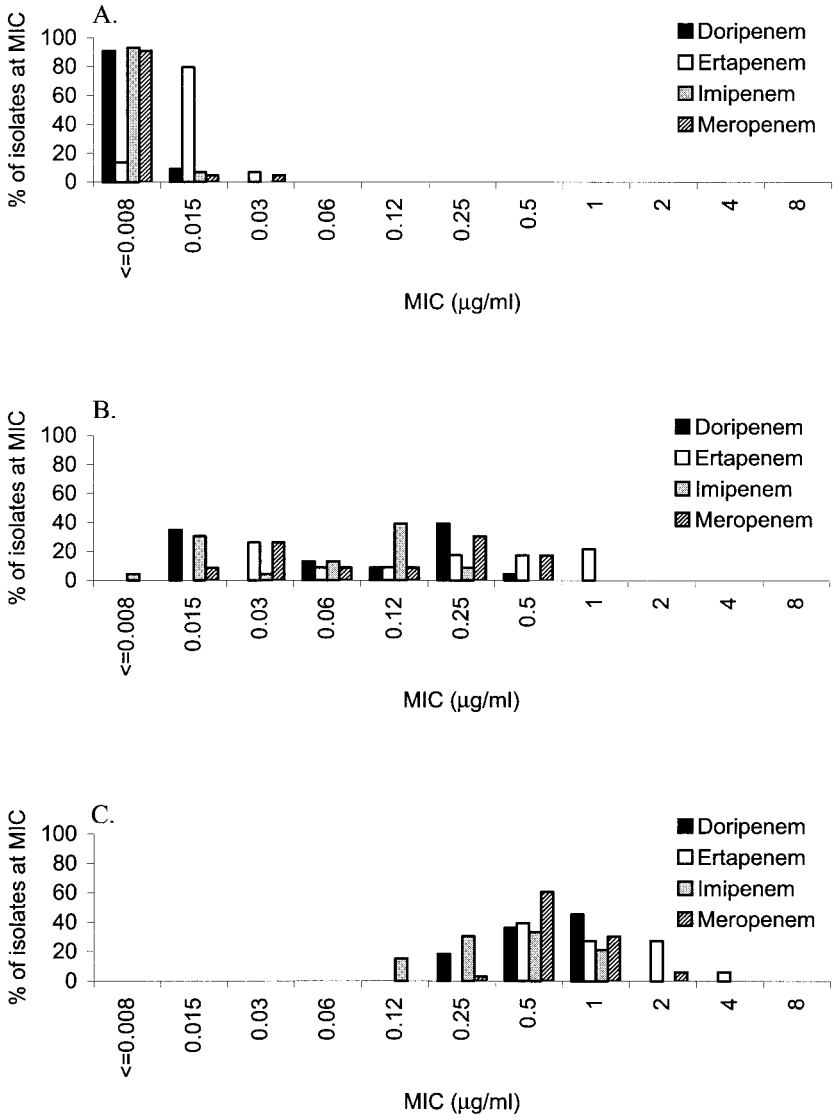

FIG. 3. MIC distributions of doripenem, ertapenem, imipenem, and meropenem against 44 isolates of penicillin-susceptible *S. pneumoniae* (A), 23 isolates of penicillin-intermediate *S. pneumoniae* (B), and 33 isolates of penicillin-resistant *S. pneumoniae* (C).

dilutions higher than for ceftazidime-susceptible isolates. Generally, the differences in the MICs of ertapenem for ceftazidime-susceptible and ceftazidime-intermediate and -resistant isolates of *Enterobacteriaceae* were greater (2 to 6 doubling dilutions for all species tested except *Providencia* spp.) than the differences in those of doripenem, imipenem, and meropenem (Table 1). Against the isolates of *Acinetobacter baumannii* tested, doripenem demonstrated better activity against ceftazidime-susceptible isolates (MIC_{90}, 1 μg/ml) than against ceftazidime-intermediate and -resistant isolates (MIC_{90}, >16 μg/ml).

As demonstrated for ertapenem, imipenem, and meropenem, doripenem showed limited activity against enterococci (Table 1). Doripenem was more active against both vancomycin-resistant and vancomycin-susceptible isolates of *Enterococcus faecalis* (MIC_{90}, 8 μg/ml) than against *Enterococcus faecium* (MIC_{90}, >32 μg/ml).

Doripenem was more active against oxacillin-susceptible isolates (MIC_{90}s, 0.03 to 0.12 μg/ml) than against oxacillin-resistant isolates (MIC_{90}s, 4 to 32 μg/ml) of *Staphylococcus aureus*, *Staphylococcus epidermidis*, and coagulase-negative staphylococci other than *S. epidermidis* (Table 1). The MICs of doripenem for staphylococci were similar to those of imipenem and lower than those of ertapenem and meropenem. The MICs of all of the carbapenems including doripenem (Fig. 2) and the other β-lactams tested were higher for oxacillin-resistant staphylococci than for oxacillin-susceptible staphylococci.

Doripenem, ertapenem, imipenem, and meropenem MIC_{90}s were all ≤0.008 μg/ml for *Streptococcus pyogenes* (Table 1). For *Streptococcus agalactiae*, the MIC_{90}s of doripenem (0.015 μg/ml) and imipenem (0.015 μg/ml) were lower than those of ertapenem (0.06 μg/ml) and meropenem (0.03 to 0.06 μg/ml). For penicillin-susceptible *Streptococcus pneumoniae*, the MIC_{90}s of doripenem, meropenem, imipenem, and ertapenem

were ≤0.015 μg/ml; for penicillin-resistant *S. pneumoniae*, the MIC_{90}s of all four carbapenems were 1 to 2 μg/ml (Table 1). The MIC distributions of doripenem, ertapenem, and imipenem were similar for penicillin-susceptible, penicillin-intermediate, and penicillin-resistant *S. pneumoniae* (Fig. 3); however, the MICs of ertapenem and meropenem were higher for all three subgroups of *S. pneumoniae*. For penicillin-susceptible and penicillin-resistant isolates belonging to the viridans group streptococci, the MIC_{90}s of doripenem (penicillin-susceptible, 0.06 μg/ml; penicillin-resistant, 4 μg/ml), imipenem (0.06 μg/ml; 2 μg/ml), and meropenem (0.06 μg/ml; 4 μg/ml) were lower than those of ertapenem (0.25 μg/ml; 8 μg/ml). Expanded-spectrum cephalosporins and piperacillin-tazobactam were not as potent as doripenem, imipenem, and meropenem against both penicillin-susceptible and penicillin-resistant isolates.

Overall, doripenem demonstrated in vitro activity similar to that of meropenem against gram-negative isolates and similar to that of imipenem against gram-positive isolates, confirming results reported by other investigators (6, 9, 11) (Table 1). Isolates of *Enterobacteriaceae* harboring ESBLs and/or inducible or derepressed AmpC β-lactamases are not associated with increased MICs of doripenem, imipenem, and meropenem relative to β-lactamase-free control isolates (S. Mushtaq, Y. Ge, and D. M. Livermore, Abstr. 43rd Intersci. Conf. Antimicrob. Agents Chemother., abstr. F-529, 2003; H. Huynh, P. R. Rhomberg, and R. N. Jones, Abstr. 43rd Intersci. Conf. Antimicrob. Agents Chemother., abstr. F-528, 2003) (Table 1). Doripenem, like all known carbapenems, is inactive against isolates of *Enterobacteriaceae* containing carbapenemases (S. Mushtaq et al., 43rd ICAAC; H. Huynh et al., 43rd ICAAC). Other preliminary studies have reported that doripenem has potent in vitro activity against *Haemophilus influenzae*, *Moraxella catarrhalis*, *Aeromonas* spp., *Bacillus* spp., *Bordetella pertussis*, and common gram-positive and gram-negative anaerobic bacteria and less or no activity in vitro against *Cornynebacterium* spp. and *Stenotrophomonas maltophilia* (6, 9, 11; R. N. Jones et al., 43rd ICAAC). Doripenem has also been reported to demonstrate activity against *P. aeruginosa* that is as potent as, or slightly more potent than, that of meropenem and imipenem (6, 9, 11; R. N. Jones et al., 43rd ICAAC).

Very limited animal study and clinical trial data have been published on doripenem (9; A. Saito, T. Inamatsu, and J. Shimada, Abstr. 37th Intersci. Conf. Antimicrob. Agents Chemother., abstr. F-219, 1997; D. A. Thye et al., 43rd ICAAC). In humans, approximately 60 to 75% of doripenem administered intravenously was recovered in the urine within 24 h (11; K. Shiba et al., 37th ICAAC; D. A. Thye et al., 43rd ICAAC) and maximum concentrations in serum of approximately 50 μg/ml were achieved following a 1,000-mg dose of doripenem given as an infusion over 1 h (D. A. Thye et al., 43rd ICAAC). Doripenem has not demonstrated the adverse effects associated with other carbapenems (renal toxicity and neurotoxicity) in two animal models (9) and in humans (D. A. Thye et al., 43rd ICAAC). Doripenem has also been reported to have a weaker neurological side-effect profile than imipenem and meropenem in an animal model (S. Hori, J. Sato, M. Kawamura, and J. Shimada, Abstr. 37th Intersci. Conf. Antimicrob. Agents Chemother., abstr. F-220, 1997).

Based upon the data generated in the present study, as well as on published data in other preliminary studies (6, 9, 11), further investigation of doripenem as a broad-spectrum parenteral agent is warranted.

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