Comparative Activities of Doripenem versus Isolates, Mutants, and Transconjugants of *Enterobacteriaceae* and *Acinetobacter* spp. with Characterized β-Lactamases

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Doripenem (S-4661), a new parenteral carbapenem, was tested against over 250 clinical isolates, mutants, and transconjugants of *Enterobacteriaceae* and *Acinetobacter* spp., selected or derived for their β-lactamase expression characteristics. Imipenem, meropenem, and ertapenem were tested as comparators, along with cephalosporins and piperacillin-tazobactam, by using National Committee for Clinical Laboratory Standards agar dilution methodology. Doripenem MICs were from 0.03 to 0.25 μg/ml for *Klebsiella* isolates, irrespective of the presence of extended-spectrum β-lactamases (ESBLs) or plasmid-mediated AmpC or hyperproduced K1 β-lactamase. Similarly, MICs of doripenem for both AmpC-inducible and -derepressed *Enterobacter* isolates were 0.06 to 0.5 μg/ml. ESBL production did not raise the MICs of doripenem for *Escherichia coli* transconjugants, and studies with known expression mutants confirmed that neither inducible nor depressed AmpC β-lactamase expression was protective in *Enterobacter cloacae*, *Citrobacter freundii*, *Serratia marcescens*, or *Morganella morganii*. In all of these respects, doripenem resembled meropenem and imipenem, whereas the MICs of ertapenem were raised (but still ≤1 μg/ml) for many ESBL-producing klebsiellas and AmpC-derepressed *E. cloacae* and *C. freundii* strains. Resistance to all carbapenems, including doripenem (MICs of mostly 16 to 64 μg/ml, compared with 0.25 to 1 μg/ml for typical strains), was seen in *Acinetobacter* isolates with metallo-β-lactamases or OXA-carbapenemases. Isolates of *Klebsiella* and *Serratia* spp. with IMP, KPC, and SME β-lactamases also were resistant to doripenem (MICs, 8 to >64 μg/ml) and to other carbapenems, although the continued apparent susceptibility (MICs, ≤0.5 μg/ml) of *E. coli* derivatives with cloned IMP-1 and NMC-A β-lactamases suggested that carbapenem resistance might require other factors besides the enzymes.

Broad-spectrum activity coupled with stability to AmpC and extended-spectrum β-lactamases (ESBLs) makes the carbapenems an extremely attractive class of antibiotics for further development (6). An additional advantage is that carbapenems, unlike extended-spectrum cephalosporins, do not select AmpC-derepressed mutants from inducible populations (3).

Doripenem (formerly S-4661; Fig. 1) (16, 17, 19) is a novel parenteral carbapenem analogue developed by Shionogi and Co., Ltd. Doripenem displays broad-spectrum activity against gram-positive and gram-negative bacteria both in vitro and in vivo (T. Nishino, M. Otsuki, M. Izawa, Abstr. 36th Intersci. Conf. Antimicrob. Agents Chemother., abstr. F-115, 1996; K. Yamaguchi and J. Shimada, Abstr. 37th Intersci. Conf. Antimicrob. Agents Chemother., abstr. S-4661, 1997). Like existing carbapenems, it has a *trans*-configured 6-hydroxyethyl, and like meropenem and ertapenem, but not imipenem, has a 1-β-methyl substituent, which protects against hydrolysis by renal dehydropeptidase I (8). The 2′ substituent is similar to that of meropenem, but is more polar, with a free amino group.

The present studies assessed the in vitro activity of doripenem against isolates, mutants, and transconjugants of *Enterobacteriaceae* and *Acinetobacter* spp. with known β-lactamases and β-lactamase expression, seeking to determine its activity against such strains and to identify whether it shares the excellent β-lactamase stability of existing carbapenems, which were tested in parallel.

MATERIALS AND METHODS

Test strains. (i) Resistant clinical isolates and controls. The *Klebsiella pneumoniae* and *Klebsiella oxytoca* isolates were collected from intensive care unit patients in western and southern Europe during surveys in 1994 (13) and 1997 to 1998 (2). They included 50 isolates inferred to have ESBLs on the basis of ceftazidime/ceftazidime-clavulanate MIC ratios of ≥16, 21 *K. oxytoca* isolates with hyperproduction of K1 enzyme, and five klebsiellas with plasmid-mediated AmpC enzymes. Ten wild-type *Klebsiella* isolates, from the same surveys but without these resistance mechanisms, were used as controls: these isolates were susceptible to extended-spectrum cephalosporins at ≤2 μg/ml and gave ceftazidime/ceftazidime-clavulanate MIC ratios of ≤ 4. AmpC-derepressed *Enterobacter* spp. and cephalosporin-susceptible *Enterobacter* control strains were obtained from recent British and Irish surveys or were reference submissions. Isolates of carbapenemase-producing *Enterobacteriaceae* comprised (i) *S. marcescens* S6 with SME-1 enzyme (24); (ii) recent clinical isolates of *K. pneumoniae* with KPC-3 enzyme (P. Tierno, Jr., L. Tysall, M.-F. Palepou, K. Young, R. Painter, D. Suber, D. Shungu, L. Silver, K. Inglima, J. Kornblum, N. Woodford, and D. Livermore, Abstr. 43rd Intersci. Conf. Antimicrob. Agents. Chemother., poster C2-50, 2003); and (iii) porin-sufficient and -deficient variants of *K. pneumoniae* K4181, a clinical isolate from Singapore with the IMP-1 metallo-β-lactamase (T. H. Koh, L. H. Sng, G. S. Babini, N. Woodford, D. M. Livermore, and L. M. Hall, Letter, Antimicrob. Agents Chemother. **45:**1939-1940, 2001). The carbapenem-resistant *Acinetobacter* isolates included those from the United

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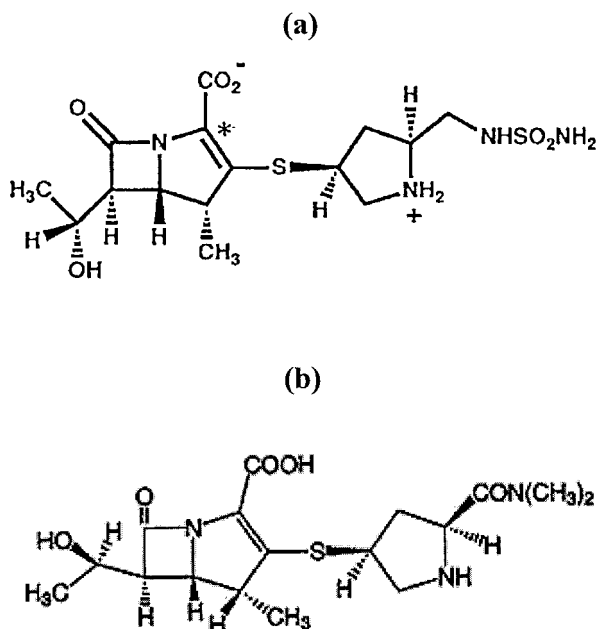
(a)

(b)

FIG. 1. Structures of doripenem (a) and meropenem (b).

Kingdom and Hong Kong with IMP metallo-β-lactamases (4, 20) and isolates collected worldwide with OXA carbapenemases (1, 5, 14). Carbapenem-susceptible *Acinetobacter* isolates were controls from a recent United Kingdom survey (7). *Escherichia coli* ATCC 25922 was a general control.

(ii) **Chromosomal β-lactamase expression mutants.** The isolates of the chromosomal β-lactamase expression mutant series of *Enterobacter cloacae*, *Citrobacter freundii*, *Serratia marcescens*, *Morganella morganii*, and *Proteus vulgaris* were described previously (12, 23). Most of these mutant series comprised a β-lactamase-inducible parent isolate together with its AmpC-derepressed and basal mutants, but some lacked an inducible strain, having been derived from isolates that were already derepressed when first cultured from patients. The β-lactamases of these species are AmpC types, except that *P. vulgaris* has a class A chromosomal enzyme.

(iii) **Escherichia coli transconjugants.** Transconjugants of *E. coli* K-12 J53 and J62, DH5-α, and JM83/109 with various plasmid-mediated β-lactamases were described previously (12) and were prepared by plate or broth mating or, in a few cases, by cloning and transformation.

Susceptibility tests. MICs were determined by the National Committee for Clinical Laboratory Standards (NCCLS) agar dilution method (18). The drugs tested comprised doripenem (lot no. CF 2066, manufactured by Shionogi and Co., Ltd., Osaka, Japan), ertapenem and imipenem (Merck, Hoddesdon, Hertfordshire, United Kingdom), meropenem (AstraZeneca, Macclesfield, Cheshire, United Kingdom), ceftazidime (GlaxoSmithKline, Stevenage, Hertfordshire, United Kingdom), cefepime (Bristol Myers Squibb, Hounslow, Middlesex, United Kingdom), piperacillin and tazobactam (Wyeth, Taplow, Berkshire, United Kingdom), and ampicillin (Sigma, Poole, Dorset, United Kingdom). Tazobactam was used at a fixed concentration of 4 μg/ml in combination with piperacillin.

RESULTS

***Klebsiella* spp. with ESBLs, AmpC β-lactamases, or hyperproduced K1 enzyme.** MIC distributions for *Klebsiella* isolates with ESBLs, plasmid-mediated AmpC enzymes, or hyperproduced K1 β-lactamase are shown in Table 1, together with MICs for control isolates with none of these mechanisms. MICs of doripenem were similarly distributed for all these groups, with modal values of 0.03 to 0.06 μg/ml and with no trend for β-lactamase producers to be less susceptible than the controls. Likewise, the MIC distributions for meropenem and imipenem were independent of ESBLs, AmpC, or hyperproduced K1 enzyme. In contrast, ertapenem MICs for ESBL-

positive *Klebsiella* isolates were scattered from 0.03 to 1 μg/ml, whereas values for ESBL-negative isolates were clustered around 0.03 μg/ml, confirming earlier results that ESBLs are associated with raised (although still low) MICs of this carbapenem (11, 12). ESBL producers were resistant to aztreonam and cephalosporins or had greatly reduced susceptibility, whereas the MIC distribution of piperacillin-tazobactam was bimodal, with some producers susceptible, with MICs of 2 ± 4 to 16 ± 4 μg/ml, while others were highly resistant, with MICs of >64 ± 4 μg/ml. Ampicillin was predictably inactive, because *Klebsiella* spp. have chromosomal SHV-1 or K1 enzymes that hydrolyze this drug (G. S. Babini and D. M. Livermore, Letter, Antimicrob. Agents Chemother. **44:**2230, 2000.).

***Enterobacter* isolates with derepressed AmpC β-lactamases.** MIC distributions for 21 AmpC-derepressed *Enterobacter* isolates are shown in Table 1, together with those for 10 control isolates with inducible AmpC. The modal MICs of doripenem (0.06 μg/ml), meropenem (0.03 to 0.06 μg/ml), and imipenem (0.12 to 0.5 μg/ml) were only slightly different between the two groups of organisms, whereas ertapenem MICs for the derepressed organisms were raised four- to eightfold. Predictably, derepression was associated with resistance to ceftazidime, aztreonam, and piperacillin and with reduced susceptibility to cefepime.

Activity against *Enterobacteriaceae* with carbapenemases. MICs for isolates with KPC-3, SME-1, and IMP-1 enzymes are shown in Table 2. The four *K. pneumoniae* isolates with KPC-3 were from separate patients in a single outbreak; the two *K. pneumoniae* isolates with IMP were variants of a single strain (K4181) and had similar specific activities against imipenem, but differed in expression of a major outer membrane protein, putatively a porin (Koh et al, Letter). All of these isolates were substantially resistant to doripenem (MICs, 8 to >64 μg/ml) and to other carbapenems. MICs of doripenem, like those of other carbapenems, were lower (16 μg/ml compared with >64 μg/ml) for the porin-expressing variant of the IMP-1$^+$ *K. pneumoniae* strain K4181. Except for *S. marcescens* S6, with SME-1 enzyme, the carbapenemase-producing strains were broadly resistant to the noncarbapenem agents tested.

Activity versus chromosomal β-lactamase-inducibility mutants of *Enterobacteriaceae*. Derepression of AmpC in laboratory mutants was not associated with any general increase in the MICs of doripenem, imipenem, and meropenem (Table 3). Minor exceptions were derepression-associated rises in the doripenem MIC for the *C. freundii* C12 and *M. morganii* M6 series, although not in any other *C. freundii* or *M. morganii* series. MICs of doripenem, imipenem, and meropenem for the AmpC-deficient mutants were equal to or slightly below those for the inducible and derepressed variants, further confirming that AmpC enzymes did not protect significantly, irrespective of their mode of expression. MICs of ertapenem were mostly raised for the derepressed variants in the *C. freundii* and *E. cloacae* series, often by a factor of four- to eightfold (Table 3). Derepression of AmpC in *E. cloacae* and *C. freundii* also was associated with sharply raised MICs of aztreonam and ceftazidime and with smaller rises in the MICs of cefepime, whereas the behavior of piperacillin-tazobactam varied with the strain. Derepression in *S. marcescens* was associated with raised MICs of aztreonam, ceftazidime, and (although less so) cefepime;

TABLE 1. MICs for isolates of *Klebsiella* and *Enterobacter* spp. with β-lactamase-mediated resistance

Isolate (*n*) and agent	MIC (μg/ml)[a]												
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	>64
Klebsiella spp.													
ESBL producers (50)													
Doripenem	11	**22**	12	5									
Meropenem	22	**28**											
Imipenem			13	**18**	12	9	2						
Ertapenem	10	**31**	3	4	1	1							
Piperacillin-tazobactam								4	**13**	14	2	1	**16**
Aztreonam								1	2	4	3	2	**38**
Ceftazidime										1	6	6	**37**
Cefepime					1	2	9	**15**	12	5	4	0	2
Ampicillin													**50**
AmpC producers (5)													
Doripenem	2	**3**											
Meropenem	**4**	1											
Imipenem			1	4									
Ertapenem		2	**3**										
Piperacillin-tazobactam										2	2		1
Aztreonam							2	2		1			
Ceftazidime												2	3
Cefepime			1	1	**2**	1							
Ampicillin													5
K. oxytoca K1 hyperproducers (21)													
Doripenem	2	**17**	1	1									
Meropenem	5	**15**	1										
Imipenem			2	**11**	7	1							
Ertapenem	**11**	8	2										
Piperacillin-tazobactam													21
Aztreonam									1	2		1	17
Ceftazidime				1	7	7	5	1					
Cefepime					3	1	**5**	4	6	1			
Ampicillin													21
Control (10)													
Doripenem	2	**7**	1										
Meropenem	**10**												
Imipenem				7	3								
Ertapenem	**10**												
Piperacillin-tazobactam									6	2			2
Aztreonam		3	**5**	2									
Ceftazidime			**5**	3	2								
Cefepime	3	**5**	2										
Ampicillin												1	**9**
Enterobacter													
AmpC-derepressed (21)													
Doripenem		**17**	2	1	1								
Meropenem	5	**14**		2									
Imipenem			7	7	6		1						
Ertapenem		1	3	**6**	7	4							
Piperacillin-tazobactam									3	2	6		**10**
Aztreonam									6	3	4	5	3
Ceftazidime													
Cefepime			2	4	4	1	5	1	1	2		1	
Ampicillin													21
AmpC-inducible (10)													
Doripenem	2	8											
Meropenem	**9**	1											
Imipenem			1	2	**4**	2	1						
Ertapenem	**6**	3	1										
Piperacillin-tazobactam						1	**7**			2			
Aztreonam	2	**3**	2	1		1							
Ceftazidime			1	**5**	1	2		1					
Cefepime	2	**5**	1	1									
Ampicillin										2		3	**6**

[a] Modal MICs are given in boldface.

TABLE 2. MICs for wild-type isolates of *Enterobacteriaceae* with carbapenemases

Isolate	Species	Phenotype	MIC (µg/ml)[a]								
			DOR	MEM	IMP	ERT	PTZ	AZT	CAZ	CPM	AMP
CL5761[b]	*Klebsiella* spp.	KPC-3	16	64	64	>64	>64	>64	64	64	>64
CL5762A[b]	*Klebsiella* spp.	KPC-3	8	32	16	16	>64	>64	64	64	>64
CL5762B[b]	*Klebsiella* spp.	KPC-3	32	64	64	>64	>64	>64	64	64	>64
CL5763[b]	*Klebsiella* spp.	KPC-3	64	>64	>64	>64	>64	>64	>64	64	>64
S6	*S. marcescens*	SME-1	32	32	>64	64	8	32	0.5	0.06	>64
K4181[c]	*K. pneumoniae*	IMP-1 porin⁻	64	>64	>64	>64	>64	>64	>64	>64	>64
K4181[c]	*K. pneumoniae*	IMP-1 porin⁺	16	16	16	16	>64	>64	>64	>64	>64

[a] AMP, ampicillin; AZT, aztreonam; CAZ, ceftazidime; CPM, cefepime; DOR, doripenem; ERT, ertapenem; IMP, imipenem; MEM, meropenem.
[b] Multiple isolates from a single outbreak.
[c] Porin-expressing and deficient variants of the same strain (10).

derepression in *M. morganii* was associated with resistance to ceftazidime but not aztreonam, cefepime, or piperacillin-tazobactam. Derepression in of *P. vulgaris* conferred only small rises in the MICs of the compounds tested here, but it has more effect on cefotaxime and ceftriaxone (22).

***E. coli* transconjugants.** MICs for *E. coli* transconjugants and their host strains are shown in Table 4. Transconjugants prepared by plate and broth mating were in *E. coli* K-12 J53 or J62 hosts: those with the IMP-1 and NMC-A carbapenemases, which required cloning, were prepared in DH5-α and JM109, respectively. None of the TEM, SHV, or OXA enzymes affected activity of the carbapenems, and MICs of these agents were as frequently slightly below as they were slightly above those for the plasmid-free hosts. In contrast, the MICs of ampicillin were raised for all the transconjugants, and those of the cephalosporins were raised for transconjugants with TEM- and SHV-type ESBLs. The TEM-1 producer was surprisingly resistant to piperacillin-tazobactam, perhaps reflecting its high level of enzyme synthesis. *E. coli* derivatives with the cloned IMP and NMC carbapenemases showed small but perceptible increases in MICs of all of the carbapenems, supporting the view that these enzymes offer only limited protection in fully-permeable organisms such as these hosts. IMP-1 was also associated with resistance to ceftazidime and slightly raised MICs of cefepime and piperacillin-tazobactam. NMC-A, in contrast, was associated with small rises in the MICs of aztreonam and piperacillin-tazobactam, but not those of ceftazidime and cefepime.

***Acinetobacter* spp. with carbapenemases.** MICs for *Acinetobacter* isolates are summarized in Table 5. All of the carbapenemase producers were resistant to doripenem as well as to other carbapenems (MICs, 8 to >64 µg/ml). Most were resistant to all of the comparator β-lactams too, although two (A1411 with IMP-1 and 74510 with IMP-4) were susceptible to piperacillin-tazobactam, perhaps due to inherent susceptibility to tazobactam, and several had marginal susceptibility (MICs of 8 µg/ml) to aztreonam and cefepime. The control *Acinetobacter* strains, which lacked carbapenemases, were susceptible to doripenem as well as imipenem and meropenem at 0.12 to 2 µg/ml, were less susceptible to ertapenem (MIC, 1 to 16 µg/ml), and showed wide MIC ranges for the other comparators, with frank resistance being frequent.

DISCUSSION

Doripenem behaved very similarly to meropenem, which it resembles in structure (19). Its MICs for control wild-type *Enterobacteriaceae* were identical (±1 dilution) to those of meropenem, were slightly lower than those of ertapenem, and were four- to eightfold below those of imipenem. MICs for isolates, transconjugants, and mutants with (i) classical TEM, SHV, and OXA enzymes; (ii) TEM and SHV ESBLs; (iii) plasmid-mediated or stably derepressed AmpC enzymes; and (iv) hyperproduced K1 enzyme were no higher than those for control strains lacking these characteristics. In all of these aspects, doripenem behaved similarly to meropenem and imipenem, whereas MICs of ertapenem for many ESBL producers and AmpC-derepressed *Enterobacter* and *C. freundii* isolates and mutants were raised. This difference between ertapenem and other carbapenems is in keeping with previous results (9, 11, 12). Unlike with cephalosporins, however, there is no substantial inoculum effect for ESBL producers with ertapenem (12), and there is no trend toward reduced susceptibility among laboratory transconjugants with ESBLs (Table 4). Production of ESBLs and hyperproduction of K1 and AmpC enzymes was associated with the expected ranges of resistance to cephalosporins, aztreonam, and piperacillin-tazobactam; minor differences between the MICs published here and those found previously (for example, see reference 23) probably reflect use of NCCLS methodology here versus local or British Society for Antimicrobial Chemotherapy methodology previously.

Isolates of *Enterobacteriaceae* with IMP, KPC, and SME carbapenemases were resistant to doripenem, imipenem, ertapenem, and meropenem and—in most cases—also to other β-lactams. It is therefore reasonable to assume that doripenem, like other carbapenems, is a substrate for these enzymes. In contrast to the carbapenem resistance of these carbapenemase-producing isolates, *E. coli* derivatives with cloned IMP-1 and NMC-A showed only small reductions in susceptibility to carbapenems. This difference presumably reflects the greater permeability of the *E. coli* host strains; the DH5-α recipient used for IMP-1, in particular, was exquisitely susceptible to β-lactams, implying considerable permeability. More generally, it has been noted that many *bla*$_{IMP}$ and *bla*$_{VIM}$-positive *Enterobacteriaceae* (and some nonfermenters) remain susceptible to established carbapenems at 1 to 2 µg/ml, implying that substantive resistance requires additional factors (21), Notable

TABLE 3. MICs for AmpC inducibility mutant series of *Enterobacteriaceae*

Strain[a]	MIC (μg/ml)[b]								
	DOR	MEM	IMP	ERT	PTZ	AZT	CAZ	CPM	AMP
C. freundii									
C2	0.06	0.03	0.5	0.015	2	0.25	0.5	0.06	>64
C2-CON	0.06	0.03	0.25	0.125	32	16	32	1	>64
C2-DEF	0.06	0.015	0.25	<0.008	2	0.125	0.5	0.06	16
C4	0.125	0.03	1	0.015	16	1	2	0.06	>64
C4-CON	0.03	0.03	0.5	0.03	4	4	32	0.125	>64
C4-DEF	0.06	0.03	0.5	<0.008	1	0.125	1	<0.03	32
C10	0.03	0.015	0.5	<0.008	4	0.06	0.25	<0.03	32
C10-CON	0.03	0.03	0.5	0.03	8	4	32	0.06	>64
C10-DEF	0.03	0.015	0.06	<0.008	1	0.06	0.125	<0.03	4
C12	0.03	0.015	0.25	<0.008	4	0.125	0.5	<0.03	16
C12-CON	0.125	0.06	1	0.06	8	4	32	0.06	>64
C12-DEF	<0.008	<0.008	0.06	<0.008	1	0.06	0.25	<0.03	4
E. cloacae									
84-CON	0.06	0.06	0.25	0.5	32	64	>64	2	>64
84-DEF	0.03	0.015	0.25	<0.008	4	0.5	1	0.06	64
100-CON	0.06	0.03	0.25	0.015	2	2	2	0.06	>64
100-DEF	<0.008	<0.008	<0.03	<0.008	<0.125	<0.03	<0.03	<0.03	0.5
684	0.06	0.03	0.5	0.03	4	0.125	0.5	0.125	>64
684-CON	0.06	0.06	0.25	0.25	32	32	64	1	>64
684-DEF	0.06	0.015	0.25	<0.008	2	0.06	0.125	<0.03	4
S. marcescens									
S2	0.06	0.03	2	0.03	16	0.125	0.125	0.06	>64
S2-CON	0.06	0.03	1	0.03	>64	4	2	1	>64
S2-DEF	0.06	0.03	2	0.015	16	0.125	0.25	0.06	>64
S7	0.06	0.03	0.25	0.03	16	0.125	0.125	0.125	>64
S7-CON	0.06	0.03	1	0.03	32	8	2	1	>64
S7-DEF	0.125	0.06	2	0.03	16	0.125	0.25	0.125	>64
M. morganii									
M1	0.5	0.125	4	0.03	0.25	<0.03	0.06	<0.03	>64
M1-CON	0.5	0.125	2	0.03	<0.125	0.5	4	<0.03	>64
M1-DEF	0.25	0.06	1	<0.008	0.25	<0.03	0.06	<0.03	4
M3-CON	0.5	0.125	2	0.03	0.5	0.5	16	<0.03	>64
M3-DEF	0.25	0.06	2	0.015	0.25	<0.03	0.06	<0.03	2
M6	0.06	0.03	1	0.015	0.25	<0.03	0.06	<0.03	64
M6-CON	0.5	0.125	2	0.03	0.25	0.05	8	<0.03	>64
M6-DEF	0.25	0.06	1	0.015	0.25	<0.03	0.06	<0.03	4
P. vulgaris									
VA1	0.5	0.125	4	0.03	1	0.06	0.125	0.125	>64
VA1-CON	0.25	0.06	2	0.015	0.5	0.06	0.125	0.125	>64
VA1-DEF	0.125	0.03	0.5	<0.008	0.5	<0.03	<0.03	<0.03	32
V2	0.25	0.06	2	0.015	1	<0.03	0.06	0.125	>64
V2-CON	0.125	0.03	1	0.015	1	0.06	0.125	0.25	>64
V2-DEF	0.125	0.03	1	0.015	0.5	<0.03	<0.03	0.06	32
V3	0.25	0.06	2	0.015	0.5	<0.03	<0.03	0.06	>64
V3-CON	0.25	0.06	2	0.015	0.5	0.125	0.125	0.25	>64
V3-DEF	0.25	0.06	1	0.015	0.5	0.06	0.06	0.06	32

[a] CON, constitutively hyperproducing AmpC enzyme irrespective of induction; DEF, deficient: making only a trace amount of AmpC enzyme irrespective of induction.
[b] Abbreviations for antibiotics are as defined in Table 2.

TABLE 4. MICs for *E. coli* strains with plasmid-mediated and cloned β-lactamases

Host	β-Lactamase	MIC (μg/ml)[a]								
		DOR	MEM	IMP	ERT	PTZ	AZT	CAZ	CPM	AMP
Plasmid carrying										
J53	OXA-1	0.015	0.015	0.125	<0.008	2	0.06	0.125	0.25	>64
J53	OXA-2	0.015	0.015	0.125	<0.008	4	0.06	0.25	0.06	>64
J53	OXA-3	0.03	0.03	0.25	0.015	4	0.125	0.5	<0.03	>64
J62	OXA-10	0.03	0.015	0.125	0.015	2	0.125	0.125	0.03	>64
J53	SHV-1	0.06	0.015	0.25	<0.008	32	0.125	0.5	0.125	>64
J53	SHV-2	0.03	0.03	0.125	0.25	>64	16	32	32	>64
J53	SHV-3	<0.008	<0.008	<0.03	<0.008	0.5	<0.03	0.06	<0.03	64
J53	SHV-4	0.125	0.03	1	0.015	8	>64	>64	8	>64
J53	SHV-5	0.06	0.03	0.5	0.015	4	>64	>64	2	>64
J62	TEM-1	0.06	0.03	0.5	0.015	64	0.125	0.25	0.125	>64
J53	TEM-2	0.015	<0.008	<0.03	<0.008	1	0.06	0.06	0.06	>64
J62	TEM-3	0.03	0.015	0.125	0.015	2	4	16	0.5	>64
J53	TEM-6	0.03	0.015	0.125	0.015	4	16	>64	1	>64
J53	TEM-9	0.06	0.03	0.25	0.03	4	>64	>64	16	>64
J53	TEM-10	0.06	0.03	0.125	0.015	4	64	>64	2	>64
JM109	NMC-A	0.5	1	2	2	16	1	0.125	<0.03	64
DH5-α	IMP-1	0.125	0.125	0.5	0.125	8	<0.03	16	0.25	32
Plasmid free										
DH5-α	R-	<0.004	0.03	<0.015	0.008	2	<0.03	0.06	<0.03	2
J53-1	R-	0.03	0.03	1	0.008	4	0.125	0.125	0.06	2
J62-1	R-	0.06	0.03	0.25	0.008	4	<0.03	0.125	<0.03	2
JM83[b]	R-	0.03	0.03	0.25	0.008	4	<0.03	0.125	<0.03	2

[a] Abbreviations are as defined in Table 2.
[b] Related to JM109, used as a host for NMC-A β-lactamase.

too, in context, was the fact that the porin-deficient variant of strain *K. pneumoniae* K4181 (IMP-1$^+$) was at least eightfold more resistant to doripenem and other carbapenems than its porin-expressing variant (Table 2). Carbapenemases have been very slow to emerge in *Enterobacteriaceae*, perhaps because they fail to give resistance except in such impermeable organisms, meaning that bacteria must sequentially acquire multiple mechanisms and go through a series of selection cycles to achieve significant resistance. Thus, only 59 out of 1.42 million

Enterobacteriaceae reported from >250 U.S. hospitals between 1996 to 2002 to the The Surveillance Network surveillance were indicated to be imipenem resistant (10), and carbapenems remain remarkably effective drugs for the treatment of the serious infections caused by *Enterobacteriaceae*, even 18 years after the launch of imipenem.

In *Acinetobacter* spp., in contrast, there is a growing problem with carbapenem resistance: some of it associated with metallo-β-lactamases, some with OXA-carbapenemases, and some

TABLE 5. MICs for *Acinetobacter* isolates with carbapenemases

Isolate no.	Carba-penemase	Source (reference)	MIC (μg/ml)[a]								
			DOR	MEM	IMP	ERT	PTZ	AZT	CAZ	CPM	AMP
A1411	IMP-1	United Kingdom (20)	16	16	8	32	<0.125	8	64	16	16
74510	IMP-4	Hong Kong (4)	32	32	32	>64	2	16	>64	64	>64
116	OXA27	Singapore (1)	32	32	64	>64	>64	32	64	16	>64
327009	OXA25	Spain (1)	>64	>64	>64	>64	>64	64	>64	64	>64
4737	OXA26	Belgium (1)	>64	>64	>64	>64	>64	32	>64	16	>64
SM28	OXA40	Spain (14)	>64	>64	>64	>64	>64	64	>64	64	>64
14BR	OXA23	Brazil (5)	32	32	>64	>64	>64	64	>64	64	>64
2002BR	OXA23	Brazil (5)	32	32	>64	>64	>64	64	>64	>64	>64
450BR	OXA23	Brazil (5)	32	32	>64	>64	>64	32	>64	>64	>64
564BR	OXA23	Brazil (5)	32	32	>64	>64	>64	32	>64	>64	>64
936BR	OXA23	Brazil (5)	64	64	>64	>64	>64	32	>64	>64	>64
801BR	OXA23	Brazil (5)	32	32	64	>64	>64	32	>64	64	>64
869BR	OXA23	Brazil (5)	32	32	>64	>64	>64	64	>64	64	>64
4131BR	OXA23	Brazil (5)	64	64	>64	>64	>64	32	>64	64	>64
Carbapenemase-negative controls (*n* = 10)											
Range		United Kingdom (7)	0.25–2	0.25–2	0.12–2	1–16	0.12–>64	1–>64	1–>64	2–64	2–>64
Mode(s)		United Kingdom (7)	0.5	1	0.5	4	64	16	4–8	4–8	>64

[a] Abbreviations are as defined in Table 2.

with carbapenemase-independent mechanisms (10), perhaps entailing target change, impermeability, or efflux. Doripenem, like meropenem and imipenem, was consistently active against carbapenemase-negative *Acinetobacter* isolates, but lacked activity against those with metallo- and OXA carbapenemases.

The present data support and extend the findings of Tsuji et al. (19), who reported that doripenem (then S-4661) had very similar in vitro activity to meropenem against a range of bacterial species, but who did not examine isolates with known modes of antibiotic resistance. Compared with imipenem, both doripenem and meropenem have greater anti-*Pseudomonas* and anti-*Proteus* activities, although with the disadvantage of being recognized by pseudomonal efflux systems (15). Ertapenem is fundamentally different in being relatively less active against nonfermenters and slightly more affected by AmpC and ESBLs (11). It is likely that doripenem will provide an alternative to imipenem and meropenem as a parenteral agent for the treatment of severe infections, including those caused by multiresistant pathogens. It is also being developed in a nebulized formulation for treatment of infections in the cystic fibrosis lung.

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