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Comparative activity of carbapenem testing: the COMPACT study

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Objectives: Doripenem is a new carbapenem recently introduced into Europe. The COMParative Activity of Carbapenem Testing (COMPACT) study compared the susceptibility of common Gram-negative bacilli causing serious infections in hospitalized patients with doripenem, imipenem and meropenem.

Methods: Gram-negative isolates (4498 total: 2171 *Pseudomonas* species; 1910 Enterobacteriaceae; and 417 other Gram-negative bacilli) were collected from 80 centres in 16 countries in Europe, the Middle East and Africa during 2008–09. The MICs of doripenem, imipenem and meropenem were determined using Etest methodology and broth microdilution. Susceptibility was interpreted according to CLSI, EUCAST and FDA breakpoints.

Results: The MIC_{90}s of doripenem, imipenem and meropenem for all isolates were 8, ≥64 and 32 mg/L, respectively. Doripenem had the lowest MIC_{90} for *Pseudomonas* species at 16 mg/L, with imipenem and meropenem values of ≥64 mg/L. Enterobacteriaceae were highly susceptible to all three carbapenems, with MIC_{90}s of doripenem, imipenem and meropenem of 0.06, 0.5 and 0.12 mg/L, respectively. Other Gram-negative isolates, predominantly *Acinetobacter baumannii*, were resistant to all three carbapenems (MIC_{90} ≥64 mg/L). Susceptibility to doripenem was observed in 14.9% of isolates resistant to imipenem and/or meropenem.

Conclusions: Doripenem showed excellent activity against Gram-negative isolates; generally it was more active than imipenem and at least as good as meropenem. Against *Pseudomonas* species, doripenem was more active than both imipenem and meropenem, with doripenem susceptibility observed for some imipenem- and/or meropenem-resistant isolates.

Keywords: doripenem, Gram-negative, imipenem, meropenem

Introduction

Pseudomonas species are a common cause of infection in hospitalized patients. Data from England, Wales and Northern Ireland, for example, show that the number of bacteraemia cases caused by *Pseudomonas* species rose to 3871 in 2007, an increase of 5.6% from 2006.[1] Enterobacteriaceae are also common causes of infection in hospitalized patients, including complicated intra-abdominal infection (cIAI), bloodstream infection (BSI) and nosocomial pneumonia (NP). *Escherichia coli*, for example, is the most common cause of BSIs, accounting for 18% of such infections in England, Wales and Northern Ireland.[2] *Acinetobacter* species play an increasing role in healthcare-associated infections as well.[2]

Data from the BSAC Bacteraemia Resistance Surveillance Programme and the Hospital Trust show dramatic shifts in carbapenem susceptibility from 2001 to 2006. There was a favourable slight downward trend in resistance of *Pseudomonas aeruginosa* to imipenem and meropenem from 2006 to 2007 (11.0% to 9.5% and 9.6% to 7.9%, respectively).[1] In Spain, one retrospective analysis of bacteraemia isolates in hospitalized patients showed *P. aeruginosa* susceptibility to imipenem to be stable from 2003 to 2005, with 0.14 episodes of imipenem resistance per 1000 patient days in 2003 compared with 0.11 episodes

per 1000 patient-days in 2005. However, ~27% of *P. aeruginosa* isolates were resistant to imipenem.[3] In Germany, on the other hand, from 2004 to 2007, resistance to meropenem increased from 2.8% to 3.4% in *P. aeruginosa* and 0.6% to 7.1% in *Acinetobacter baumannii*.[4,5] Greater shifts were observed for cephalosporins, ciprofloxacin and gentamicin against *E. coli* and *Klebsiella* species, while the carbapenems were broadly active.[6] Surveillance results from the Meropenem Yearly Susceptibility Information Collection (MYSTIC) 2007 show similar trends across Europe for *P. aeruginosa*, Enterobacteriaceae and *Acinetobacter* species, although regional differences exist.[7–9] In Turkey, for example, susceptibility of *A. baumannii* to imipenem decreased from 80.4% in 2000 to 40.0% in 2006 and to meropenem from 71.7% to 40.0% during the same time period.[10] In Spain, susceptibility of *A. baumannii* decreased from ~73% during 2001–04 to 52.2% in 2006.[11] As in previous surveys, imipenem-resistant *P. aeruginosa*, resistance caused by extended-spectrum β-lactamase- and AmpC β-lactamase-producing Enterobacteriaceae and multidrug-resistant *Acinetobacter* species remain problematic.[7] As a consequence of these trends and their geographical variability, it is important to consider current, local susceptibility patterns when selecting antimicrobial therapy in the treatment of each patient. These issues are also important considerations when determining which antibiotics to include in a formulary.

Doripenem is a carbapenem antibiotic with a spectrum of activity similar to that of other carbapenems, but the addition of a sulfamoyl-aminomethyl-pyrrolidinylthio group contributes to greater antibacterial activity, a lower potential for seizures and greater stability in solution, allowing dosing flexibility.[12] Doripenem is approved in the European Union and in some Asia–Pacific countries for treating NP, including ventilator-associated pneumonia, cIAI and complicated urinary tract infections.

The COMParative Analysis of Carbapenem Testing (COMPACT) study was conducted to evaluate the *in vitro* activity of doripenem, imipenem and meropenem against selected, recent, Gram-negative clinical isolates. In addition, the local pathogen susceptibility to doripenem, imipenem and meropenem was to be determined and compared with the general susceptibility pattern across Europe, the Middle East, Africa and Asia–Pacific. This paper reports European, Middle Eastern and African data, which were collected and analysed at each centre using Etest. Quality control was performed by a central laboratory on a selected sample as described below.

Materials and methods

Eighty centres in 16 countries (Czech Republic, Egypt, Estonia, France, Germany, Greece, Ireland, Italy, Latvia, Poland, Portugal, Russia, Slovak Republic, Spain, Turkey and the UK) were invited to prospectively collect and submit 60 non-duplicate Gram-negative isolates from intensive care unit (ICU) and non-ICU hospitalized patients with cIAI, BSI or NP, including ventilator-associated pneumonia. Repeat isolates collected from the same infection episode were excluded. Target isolates collected between May 2008 and June 2009 (and the targeted number per centre) were: *P. aeruginosa* (30); Enterobacteriaceae (24); and *Acinetobacter* or other Gram-negative pathogens (6). Each centre tested its own isolates for susceptibility to doripenem, imipenem and meropenem using Etest strips according to the manufacturer's guidelines (bioMérieux SA, Marcy l'Étoile, France).

Isolates were sent to a reference laboratory (Quotient Bioresearch Ltd, Fordham, UK) for species confirmation and storage at −70°C in undiluted horse serum. Species re-identification was carried out for all isolates submitted using the following systems: *Haemophilus influenzae*—Gram's stain, X factor (haemin) and V factor (NAD) test; *E. coli*—Gram's stain, oxidase test, PGUA (β-glucuronidase) test, 20E API Bacterial Identification System; other Enterobacteriaceae—Gram's stain, oxidase test, 20E API Bacterial Identification System; *P. aeruginosa*—Gram's stain, oxidase test, C-390 diagnostic tablet test, 20NE API Bacterial Identification System; and other non-fastidious, non-fermentative Gram-negative bacilli—Gram's stain, oxidase test, 20NE API Bacterial Identification System. Confirmatory MIC testing was carried out only for 10% of randomly selected susceptible isolates from each centre (and all resistant isolates as described below). The reference laboratory determined the MICs of doripenem, imipenem and meropenem for all isolates received and identified as resistant to at least one of the carbapenems by each centre's Etest MIC data based on FDA breakpoints for doripenem[13] (susceptible, non-susceptible) and CLSI breakpoints for imipenem and meropenem (susceptible, intermediate, resistant).[14] FDA breakpoints were used for doripenem because CLSI breakpoints were not available when the study was initiated. Similarly, CLSI 2009 breakpoints were the accepted standard at the time the study was initiated. However, the CLSI breakpoints for Enterobacteriaceae issued in June 2010 are also used in the analysis.[15] Similarly, breakpoints for doripenem were not issued by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) until after the study was initiated, but are also used in the analysis.[16]

MIC was determined by the reference laboratory using in-house panels by both broth microdilution using CLSI methodology[17] and Etest according to the manufacturer's guidelines. Growth observed at 32 mg/L using Etest was reported as MIC ≥64 mg/L. Further MIC determinations were also performed for quality control purposes on each centre's Etest results by randomly selecting 10% of susceptible isolates from each centre. Each of these isolates was tested by both broth microdilution and Etest.

Results

Isolates, patients and sites

Eighty centres in 16 countries participated in the study and submitted a total of 4641 (96.7% of the target) isolates. Of these, 4498 (96.9%) were correctly identified and eligible for inclusion and serve as the basis of this report (Table 1). One hundred and forty-three isolates were excluded because they were not viable upon arrival, ineligible species, isolated from infections not conforming to the study protocol or submitted without centre MIC data. By pathogen group, 48.3% were *Pseudomonas* species, of which 99.3% were *P. aeruginosa* (47.9% of total isolates), 42.5% were Enterobacteriaceae, of which 42.8% were *E. coli* (18.2% of total isolates) and 23.1% were *Klebsiella pneumoniae* (9.8% of total isolates), and 9.2% were other Gram-negative bacteria, of which 65.7% were *A. baumannii* (6.1% of total isolates).

NP was the most common type of infection, accounting for 40.8% of isolates, while BSI accounted for 36.6% and cIAI for 22.6%. More isolates came from non-ICU patients (54.4%) than ICU patients (45.6%).

Confirmatory MIC testing by reference laboratory

Isolates deemed to be non-susceptible to at least one carbapenem ($n=978$; 21.7% of total isolates), and a random 10% of

Table 1. Breakdown of 4498 isolates collected

Pathogen group	Species	No. of isolates (%)	Total (%)
Pseudomonas	*P. aeruginosa*	2155 (99.3)	2171 (48.3)
	others (<1% each)	16 (0.7)	
Enterobacteriaceae	*E. coli*	817 (42.8)	1910 (42.5)
	K. pneumoniae	442 (23.1)	
	E. cloacae	186 (9.7)	
	K. oxytoca	97 (5.1)	
	Proteus mirabilis	82 (4.3)	
	Enterobacter aerogenes	78 (4.1)	
	Serratia marcescens	66 (3.5)	
	Morganella morganii	32 (1.7)	
	Citrobacter freundii	26 (1.4)	
	others (<1% each)	84 (4.4)	
Other Gram-negatives	*A. baumannii*	274 (65.7)	417 (9.2)
	S. maltophilia	68 (16.3)	
	A. baumannii/calcoaceticus	14 (3.4)	
	Acinetobacter lwoffii	14 (3.4)	
	Burkholderia cepacia	11 (2.6)	
	Achromobacter xylosoxidans	7 (1.7)	
	Acinetobacter junii/johnsonii	6 (1.4)	
	Haemophilus influenzae	6 (1.4)	
	Acinetobacter junii	5 (1.2)	
	others (<1% each)	12 (2.9)	

susceptible isolates ($n=473$), underwent confirmatory testing at the reference laboratory by broth microdilution and Etest (total isolates, 1451). When comparing centre and reference laboratory susceptibility by Etest, there was good overall susceptibility category agreement (89.9% for doripenem, 95.4% for imipenem and 90% for meropenem). The percentage of centre non-susceptible isolates found to be susceptible by the reference laboratory was almost identical for the three carbapenems (11.8% for doripenem, 8.4% for imipenem and 11.0% for meropenem). Similar results for doripenem or meropenem were found for isolates susceptible by the centre Etest but non-susceptible by the reference laboratory (8.8% and 9.1%, respectively). However, a better correlation was seen for imipenem (2.2%).

Interestingly, although broth microdilution and Etest MIC determinations at the reference laboratory correlated very well overall for doripenem, imipenem and meropenem (98.3%, 98.5% and 91.7%, respectively), 14.6% of isolates non-susceptible to meropenem by Etest were susceptible by broth microdilution.

Susceptibility

The mean MIC_{90} of doripenem for all isolates was 8 mg/L, compared with ≥64 mg/L for imipenem and 32 mg/L for meropenem. The difference was attributable mainly to a 4-fold higher MIC_{90} of meropenem and imipenem compared with that of doripenem for *Pseudomonas* species and an 8-fold higher MIC_{90} of imipenem for Enterobacteriaceae.

Activity for each of the three carbapenems was highest in Ireland and lowest in Egypt and Italy (Table 2). The range of MIC_{90}s varied several-fold between countries: doripenem was lowest (0.25–≥64 mg/L); meropenem intermediate (0.5–≥64 mg/L); and imipenem highest (1–≥64 mg/L). The lowest MIC_{90} for *Pseudomonas* species for each country was generally that of doripenem, except for Ireland, where the MIC_{90}s of doripenem and meropenem were the same, and Egypt, Estonia, Italy and Russia, where the MIC_{90}s of doripenem, meropenem and imipenem were the same.

For *P. aeruginosa*, the MIC_{90} of doripenem was lowest (16 mg/L) compared with ≥64 mg/L for both imipenem and meropenem. Only 19.2% of *Pseudomonas* isolates had a doripenem MIC of >4 mg/L, compared with 34.2% for imipenem and 26.7% for meropenem (Table 3). The proportion of isolates for which the MIC of imipenem and meropenem was ≥64 mg/L was three and two times as high, respectively, as for doripenem (17.1%, 11.6% and 5.6%, respectively).

Thirty species of Enterobacteriaceae were collected: 42.8% *E. coli*; 23.1% *K. pneumoniae*; 9.7% *Enterobacter cloacae*; and 5.1% *Klebsiella oxytoca*. The remaining 26 species were collected at a frequency of <5%. Of the Enterobacteriaceae, 1.3% of isolates were non-susceptible to doripenem, 0.8% to imipenem and 0.4% to meropenem. Isolates from Egypt had the highest rates of resistance (doripenem 9.5%, imipenem 4.8% and meropenem 4.8%). The lowest MIC_{90} of doripenem (0.03 mg/L) was observed for *E. coli* and *K. oxytoca*, the lowest MIC_{90} of imipenem (0.25 mg/L) was observed for *E. coli*, *K. oxytoca* and *K. pneumoniae*, and the lowest MIC_{90} of meropenem (0.06 mg/L) was observed for *E. coli* and *K. oxytoca*.

Fifteen other Gram-negative species were collected. Of these 417 isolates, 65.7% were *A. baumannii* and 16.3% were *Stenotrophomonas maltophilia*. The remaining 13 species were collected at a frequency of <5%. The MIC_{90} of all three carbapenems for other Gram-negative isolates was ≥64 mg/L, which was due largely to an MIC_{90} of ≥64 mg/L of all three carbapenems for *A. baumannii*. Of *A. baumannii*, 58.8% of isolates were not susceptible to doripenem, 48.9% were not susceptible to imipenem and 48.2% were not susceptible to meropenem.

Based on FDA breakpoints, 844 (18.8%) isolates were deemed to be doripenem non-susceptible according to the Etest MIC results from the collecting centres. Based on EUCAST breakpoints for imipenem and meropenem, 921 (20.5%) isolates were non-susceptible to imipenem and 777 (17.3%) to meropenem. One hundred and thirty-four (3.0%) isolates that were resistant to at least one of the three carbapenems were resistant to imipenem and/or meropenem but were susceptible to doripenem. Of the 844 doripenem-non-susceptible isolates, 619 (73.3%) were also resistant to both imipenem and meropenem, 125 (14.8%) were also resistant to imipenem but not meropenem and 19 (2.3%) were also resistant to meropenem but not imipenem.

Table 2. Activity of carbapenems by country

		All pathogens			*Pseudomonas* species		
Country	Carbapenem	MIC_{50}	MIC_{90}	range	MIC_{50}	MIC_{90}	range
Czech Republic (2 centres)	doripenem	0.12	4	0.008–≥64	0.25	4	0.06–8
	imipenem	1	16	0.008–≥64	1	16	0.03–≥64
	meropenem	0.25	16	0.015–≥64	0.5	16	0.06–≥64
Egypt (1 centre)	doripenem	0.25	≥64	0.06–≥64	2	≥64	0.25–≥64
	imipenem	0.5	≥64	0.06–≥64	2	≥64	0.12–≥64
	meropenem	0.12	≥64	0.03–≥64	2	≥64	0.06–≥64
Estonia (1 centre)	doripenem	0.06	32	0.008–32	1	32	0.25–32
	imipenem	0.25	32	0.12–32	2	32	0.25–32
	meropenem	0.06	32	0.008–32	2	32	0.25–32
France (7 centres)	doripenem	0.12	8	0.004–≥64	0.5	8	0.03–≥64
	imipenem	1	≥64	0.008–≥64	2	≥64	0.12–≥64
	meropenem	0.12	16	0.004–≥64	0.5	32	0.03–≥64
Germany (7 centres)	doripenem	0.05	2	0.002–≥64	0.25	4	0.015–≥64
	imipenem	0.5	16	0.06–≥64	1	32	0.12–≥64
	meropenem	0.12	4	0.002–≥64	0.25	16	0.015–≥64
Greece (2 centres)	doripenem	0.05	8	0.004–≥64	0.12	32	0.015–≥64
	imipenem	0.5	≥64	0.015–≥64	1	≥64	0.12–≥64
	meropenem	0.12	16	0.008–≥64	0.25	≥64	0.03–≥64
Ireland (1 centre)	doripenem	0.05	0.25	0.008–8	0.12	0.5	0.015–8
	imipenem	0.25	1	0.12–≥64	1	4	0.25–≥64
	meropenem	0.12	0.5	0.015–≥64	0.12	0.5	0.015–≥64
Italy (12 centres)	doripenem	0.12	≥64	0.004–≥64	0.5	≥64	0.004–≥64
	imipenem	1	≥64	0.015–≥64	2	≥64	0.015–≥64
	meropenem	0.12	≥64	0.004–≥64	0.5	≥64	0.004–≥64
Latvia (1 centre)	doripenem	0.05	8	0.015–≥64	0.5	1	0.015–4
	imipenem	0.5	8	0.03–≥64	0.5	2	0.5–4
	meropenem	0.05	16	0.015–≥64	1	2	0.03–≥64
Poland (1 centre)	doripenem	0.05	2	0.008–4	0.25	4	0.03–4
	imipenem	0.5	16	0.12–32	2	32	0.25–32
	meropenem	0.25	16	0.008–32	1	32	0.06–32
Portugal (3 centres)	doripenem	0.12	8	0.008–≥64	0.5	8	0.06–≥64
	imipenem	1	≥64	0.06–≥64	2	≥64	0.25–≥64
	meropenem	0.25	32	0.008–≥64	1	16	0.06–≥64
Russia (7 centres)	doripenem	0.5	32	0.008–32	2	32	0.03–32
	imipenem	1	32	0.03–32	8	32	0.5–32
	meropenem	0.5	32	0.008–32	4	32	0.06–32
Slovak Republic (2 centres)	doripenem	0.03	2	0.008–≥64	0.12	8	0.03–≥64
	imipenem	0.25	8	0.06–≥64	1	≥64	0.5–≥64
	meropenem	0.06	2	0.08–≥64	0.25	≥64	0.06–≥64
Spain (16 centres)	doripenem	0.12	32	0.008–≥64	0.5	16	0.015–≥64
	imipenem	1	≥64	0.015–≥64	2	≥64	0.06–≥64
	meropenem	0.25	≥64	0.008–≥64	1	≥64	0.015–≥64

Continued

Table 2. *Continued*

Country	Carbapenem	All pathogens			*Pseudomonas* species		
		MIC_{50}	MIC_{90}	range	MIC_{50}	MIC_{90}	range
Turkey (10 centres)	doripenem	0.12	32	0.008–≥64	1	32	0.03–≥64
	imipenem	1	≥64	0.06–≥64	4	≥64	0.12–≥64
	meropenem	0.25	≥64	0.008–≥64	1	≥64	0.03–≥64
UK (5 centres)	doripenem	0.03	0.5	0.008–≥64	0.12	2	0.015–≥64
	imipenem	0.25	2	0.06–≥64	1	16	0.12–≥64
	meropenem	0.06	0.5	0.008–≥64	0.25	4	0.008–≥64

Table 3. Cumulative activity of carbapenems by pathogen group

	MIC (mg/L)															
	0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	≥64
All pathogens (*n*=4498)																
doripenem	0.0	0.2	2.1	19.1	35.5	45.8	57.3	67.1	73.0	77.8	82.1	86.3	90.0	91.7	94.0	100.0
imipenem	0.0	0.0	0.1	0.3	0.5	1.1	14.8	38.1	47.5	66.3	75.5	78.3	80.2	82.7	88.0	100.0
meropenem	0.0	0.1	1.0	14.2	31.8	41.2	52.0	61.8	69.3	74.7	78.8	82.5	85.3	87.5	91.0	100.0
Pseudomonas species (*n*=2171)																
doripenem	0.0	0.1	0.1	0.5	3.5	14.5	32.3	48.1	58.0	65.9	73.5	80.8	87.8	91.0	94.4	100.0
imipenem	0.0	0.0	0.0	0.1	0.1	0.2	1.0	2.4	10.7	44.9	61.4	65.8	69.0	73.8	82.9	100.0
meropenem	0.0	0.1	0.1	0.4	1.7	7.9	22.5	38.2	51.0	59.8	66.7	73.3	78.5	82.6	88.4	100.0
Enterobacteriaceae (*n*=1910)																
doripenem	0.1	0.4	4.8	44.4	79.0	90.4	95.5	97.7	98.7	99.3	99.6	99.7	99.8	99.8	99.9	100.0
imipenem	0.0	0.0	0.3	0.6	1.2	1.8	32.4	82.0	92.7	96.1	98.2	99.2	99.5	99.6	99.7	100.0
meropenem	0.1	0.2	2.2	32.9	72.6	87.1	95.3	97.6	98.5	99.1	99.3	99.6	99.7	99.7	99.8	100.0
Other Gram-negatives (*n*=417)																
doripenem	0.0	0.0	0.0	0.2	2.6	4.6	12.0	25.9	34.1	41.0	46.3	53.5	57.1	58.5	65.0	100.0
imipenem	0.0	0.0	0.0	0.0	0.0	2.4	6.2	23.0	31.4	41.3	44.6	47.5	49.9	51.8	60.7	100.0
meropenem	0.0	0.0	0.2	0.2	1.7	4.8	7.2	20.4	30.7	40.3	47.5	51.6	54.7	57.6	63.8	100.0

Only 773 (91.6%) of the doripenem-non-susceptible isolates were confirmed by the reference laboratory, suggesting that collecting centres might over-report carbapenem non-susceptibility. Of the doripenem-non-susceptible isolates, *Pseudomonas* species and *Acinetobacter* species were the most common, making up 68.1% and 20.3% of the non-susceptible isolates, respectively. However, 18.4% of *Pseudomonas* isolates determined as doripenem susceptible by the collecting centre using Etest were found to be doripenem non-susceptible by the reference laboratory, which suggests that under-reporting of carbapenem non-susceptibility occurred as well.

Susceptibility by infection type

NP was the most frequent type of infection (40.8%). *Pseudomonas* species were the most common cause of NP (61.1%), compared with Enterobacteriaceae (27.1%) and other Gram-negative bacilli (11.8%). For all NP pathogens, the MIC_{90} of doripenem was 32 mg/L (Table 4), compared with ≥64 mg/L for imipenem and meropenem. Except for other Gram-negative isolates, for which the MIC_{90} of all three carbapenems was ≥64 mg/L, doripenem was the most active. For *Pseudomonas* species, the MIC_{90} of doripenem was 16 mg/L, compared with ≥64 mg/L for imipenem and meropenem.

Doripenem and meropenem had MIC_{90}s of 8 and 16 mg/L, respectively, for all BSI isolates, compared with ≥64 mg/L for imipenem. Except for other Gram-negative isolates, where the MIC_{90} of all three carbapenems was ≥64 mg/L, doripenem was the most active. For *Pseudomonas* species, doripenem had the lowest MIC_{90} at 16 mg/L, compared with ≥64 mg/L imipenem and meropenem.

Enterobacteriaceae were the most common cause of cIAI (49.3%) compared with *Pseudomonas* species (44.7%) and other Gram-negative bacilli (6.0%). Against all cIAI pathogens,

the MIC_{90} of doripenem was 8 mg/L, compared with 32 mg/L and 16 mg/L for imipenem and meropenem, respectively. For *Pseudomonas* species, doripenem had the lowest MIC_{90} at 8 mg/L, compared with ≥64 mg/L for imipenem and 32 mg/L for meropenem. Against Enterobacteriaceae, doripenem and meropenem showed comparable activity and both were superior to imipenem. The MIC_{90} of all three carbapenems for all cIAI caused by other Gram-negative isolates was ≥64 mg/L.

Susceptibility by patient type

Except where too few isolates were collected, all pathogens were isolated from both ICU and non-ICU patients. More isolates were collected from non-ICU patients than ICU patients; 54.4% of all strains were isolated from non-ICU patients and 45.6% from ICU patients. Overall, doripenem was slightly more active than meropenem and imipenem against all ICU isolates combined and 4- to 8-fold more active than meropenem and imipenem, respectively, against all non-ICU isolates combined.

For all ICU isolates, as well as isolates of *Pseudomonas* species, the MIC_{90} of doripenem was 32 mg/L, compared with ≥64 mg/L for both imipenem and meropenem. The MIC_{90}s of doripenem and meropenem were the same for Enterobacteriaceae isolates (0.12 mg/L) and lower than that of imipenem (0.5 mg/L). An MIC_{90} of ≥64 mg/L of all three carbapenems was observed for other Gram-negative isolates.

Pseudomonas species and Enterobacteriaceae were observed with similar frequency in non-ICU infections (46.9% and 46.3%, respectively), compared with 6.7% for other Gram-negative isolates. For non-ICU isolates, the MIC_{90} for doripenem was 4 mg/L, compared with 32 mg/L and 16 mg/L of imipenem and meropenem, respectively. For *Pseudomonas* species, the MIC_{90}s of imipenem and meropenem were 8- and 4-fold higher than that of doripenem (≥64, 32 and 8 mg/L, respectively). For Enterobacteriaceae, the MIC_{90}s of doripenem, imipenem and meropenem were 0.06, 0.5 and 0.12 mg/L, respectively. An MIC_{90} of ≥64 mg/L of all three carbapenems was observed for other Gram-negative isolates.

Table 4. Activity of doripenem by infection type

Pathogen	Infection type	*n*	MIC_{50}	MIC_{90}	Range
All isolates	all	4498	0.12	8	0.002–≥64
	BSI	1646	0.06	8	0.002–≥64
	cIAI	1017	0.06	8	0.004–≥64
	NP	1835	0.25	32	0.004–≥64
Pseudomonas species	all	2171	0.5	16	0.004–≥64
	BSI	595	0.25	16	0.015–≥64
	cIAI	455	0.25	8	0.015–≥64
	NP	1121	0.5	16	0.004–≥64
Enterobacteriaceae	all	1910	0.03	0.06	0.002–≥64
	BSI	911	0.03	0.06	0.002–32
	cIAI	501	0.03	0.12	0.004–≥64
	NP	498	0.03	0.12	0.004–≥64
Other Gram-negatives[a]	all	417	4	≥64	0.015–≥64
	BSI	140	4	≥64	0.015–≥64
	cIAI	61	4	≥64	0.03–≥64
	NP	216	4	≥64	0.03–≥64

[a]Including *Acinetobacter* species.

Discussion

In the COMPACT surveillance study, doripenem had activity similar to or slightly better than meropenem and better activity than imipenem against the Gram-negative isolates collected in Europe, the Middle East and Africa. The wide range in susceptibility among countries for each of the three carbapenems was consistent with previous studies.[7,18] This demonstrates the importance of understanding local susceptibility patterns when treating patients and when selecting antibiotics for formulary inclusion. Similarly, pathogen source and type of infection are also key considerations. The MIC_{90} was lower for non-ICU pathogens compared with ICU pathogens, lowest for cIAI or BSI pathogens and highest for NP pathogens.

Against *Pseudomonas* species, doripenem was the most active of the three carbapenems. At an MIC of ≤2 mg/L, the FDA breakpoint for doripenem, 73.5% of *P. aeruginosa* were susceptible to doripenem, 61.4% to imipenem and 66.7% to meropenem. At ≤4 mg/L, the CLSI breakpoint for imipenem and

Table 5. Carbapenem breakpoints by agency

	FDA			CLSI						EUCAST					
	doripenem			imipenem/ meropenem			doripenem/ imipenem/ meropenem[a]			doripenem		imipenem		meropenem	
Family/genus (species)	S	I	R	S	I	R	S	I	R	S	R	S	R	S	R
P. aeruginosa	≤2	—	—	≤4	8	≥16	≤4	8	≥16	≤1	>4	≤4	>8	≤2	>8
Enterobacteriaceae	≤0.5	—	—	≤4	8	≥16	≤1	2	≥4	≤1	>4	≤2	>8	≤2	>8
Acinetobacter species	≤1	—	—	≤4	8	≥16	≤4	8	≥16	≤1	>4	≤2	>8	≤2	>8

S, susceptible; I, intermediate; R, resistant.
[a]As of June 2010.

Table 6. Susceptibilities based on agency breakpoints

	% Susceptible			% Resistant		
	FDA/CLSI[a]	CLSI[b]	EUCAST[c]	FDA/CLSI[a]	CLSI[b]	EUCAST[c]
Pseudomonas species						
doripenem	73.5	80.8	65.9	—	12.2	19.2
imipenem	65.8	65.8	65.8	31.0	31.0	31.0
meropenem	73.3	73.3	66.7	21.5	21.5	22.5
Enterobacteriaceae						
doripenem	98.7	99.3	99.3	—	0.4	0.3
imipenem	99.2	96.1	98.2	0.5	1.8	0.5
meropenem	99.6	99.1	99.3	0.3	0.7	0.3
A. baumannii						
doripenem	41.2	55.1	41.2	—	40.1	44.9
imipenem	51.1	51.1	47.8	47.1	47.1	47.1
meropenem	51.8	51.8	46.0	45.2	45.2	45.2

[a]Based on FDA breakpoints for doripenem[13] and CLSI 2009[14] breakpoints for imipenem and meropenem.
[b]Based on CLSI 2010[15] breakpoints for doripenem, imipenem and meropenem.
[c]Based on EUCAST 2010[16] breakpoints for doripenem, imipenem and meropenem.

meropenem, 80.8% were susceptible to doripenem, 65.8% to imipenem and 73.3% to meropenem.

The determination of susceptibility is dependent on the breakpoints used, which in the case of carbapenems varies somewhat based on the agency (i.e. FDA, CLSI or EUCAST) (Table 5). In general, susceptibility results are similar between the FDA and EUCAST for doripenem and between the CLSI and EUCAST for imipenem and meropenem (Table 6). However, because the breakpoints differ between the FDA,[13,18,19] CLSI[14,15] and EUCAST[16] for *P. aeruginosa*, these small differences can have important treatment implications. For example, with respect to *Pseudomonas* species for doripenem, the susceptibility changes from 73.5% (FDA) to 65.9% (EUCAST). The absolute difference of 7.6% means that a different treatment decision could be made in one of every 13 patients (7.7%) based simply on breakpoint criteria. If the current CLSI[15] and EUCAST[16] 2010 breakpoints are used, the absolute difference of 14.9% means that a different decision could be made in one of every seven patients.

Doripenem is stable at room temperature and can be given with prolonged infusion regimens. At a dosage of 500 mg every 8 h, a 4 h infusion of doripenem provides >90% probability of achieving pharmacokinetic/pharmacodynamic target attainment of 35%–40% for the exposure time for which the free drug concentration remains at the MIC ($fT>$MIC), for an MIC of 4 mg/L.[20,21] The cumulative activity of doripenem observed in this study (Table 3) suggests that there is an 80.8% probability of achieving target attainment of 40% against *Pseudomonas* spp. (MIC ≤4 mg/L) with 500 mg of doripenem every 8 h administered over 4 h. For meropenem, 1 g every 8 h administered over 3 h achieves a 99.1%–100% probability of achieving target attainment for an MIC of 4 mg/L.[22,23] Therefore, our data suggest that there is a 73.3% probability of achieving target attainment of 40% against *Pseudomonas* spp. (MIC ≤4 mg/L) with meropenem 1 g every 8 h administered over 3 h.

Doripenem and meropenem were equally active against Enterobacteriaceae and at least 4-fold more active than imipenem. These results are consistent with susceptibility data from the UK and Ireland for 2001–06[6] as well as Germany.[4,5]

All three carbapenems showed poor activity against *Acinetobacter* species. Nonetheless, many isolates of *A. baumannii* were still susceptible. With an MIC of 1 mg/L, the FDA[13] and EUCAST[16] breakpoint for doripenem, 41.2% of isolates were susceptible. At an MIC of 4 mg/L, the CLSI[15] breakpoint for imipenem and meropenem, 51.1% and 51.8% of isolates, respectively, were susceptible. With an MIC of 8 mg/L, the intermediate CLSI breakpoint for imipenem and meropenem, an additional 1.8% and 4.0%, respectively, were of intermediate susceptibility. For these additional isolates of *A. baumannii*, combination antibiotic treatment would be needed.[20,24]

Carbapenem discordance, defined as susceptibility to one carbapenem while simultaneously being non-susceptible to another carbapenem under the same breakpoint recommendations,[24] occurred in a significant percentage of isolates. Of the 897 isolates resistant to imipenem and/or meropenem in the COMPACT study, 134 were susceptible to doripenem. This discordance rate of 14.9% is higher than the 10% reported by Scheetz *et al.*,[25] although only *Pseudomonas* species were included in that study.

Doripenem showed comparable activity against isolates from BSIs and cIAIs. However, the MIC_{90} was higher for isolates from NP infections. Similarly, a higher MIC_{90} was observed for ICU compared with non-ICU isolates.

Our results for COMPACT in Europe, the Middle East and Africa are similar to those observed for COMPACT in eight Asia–Pacific countries.[26] As in Europe, doripenem was the most active of the carbapenems tested against Asia–Pacific isolates ($n=1612$). The MIC_{90} for Asia–Pacific Enterobacteriaceae isolates (40.7% of all isolates) was 0.06 mg/L for doripenem, 0.12 mg/L for meropenem and 0.5 mg/L for imipenem. For *Pseudomonas* species (48.6% of all isolates), the MIC_{90} was 8 mg/L for doripenem and ≥64 mg/L for both meropenem and imipenem. All three carbapenems showed poor activity against *A. baumannii*; all had an MIC_{90} of ≥64 mg/L. Furthermore, the Asia–Pacific results show that the MIC_{90} was lower for non-ICU compared with ICU *Pseudomonas* species.

The Etest showed good correlation with the broth microdilution technique. In the present study, the correlation was 98.3% for doripenem, 98.5% for imipenem and 91.7% for meropenem. These results are consistent with a previous investigation involving the activity of imipenem and other mostly β-lactam antibiotics against *P. aeruginosa*.[27] The correlation was good for isolates that were clearly susceptible or clearly resistant but not for those that were of intermediate susceptibility. Such a correlation was not examined in our study. It should also be noted that there was good correlation in susceptibility between the Etest results of the collecting centres and the reference laboratory, with 89.9%, 95.4% and 90.0% agreement for doripenem, imipenem and meropenem, respectively.

The carbapenems doripenem, imipenem and meropenem possess good activity against the Gram-negative isolates included in this study from Europe, the Middle East and Africa, including *Pseudomonas* species and Enterobacteriaceae. A higher rate of resistance was observed for *Acinetobacter* species, the majority of which were *A. baumannii*. There was a several-fold variation in susceptibility between the countries and susceptibility was generally greater than observed for isolates from Asia–Pacific. The activity of doripenem was found to be similar to or better than meropenem and better than imipenem.

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