

ORIGINAL ARTICLE

Antimicrobial resistance surveillance of doripenem in China

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To investigate the antibacterial resistance to doripenem in China and to understand the distribution trends of resistant bacteria. All the clinical isolates were collected from hospitals and the susceptibility tests were performed using the agar dilution method recommended by the Clinical Laboratory Standards Institute (CLSI) central laboratory. The susceptibility of the isolates to antimicrobial agents was determined using the CLSI (2014) or European Committee on Antimicrobial Susceptibility Testing (EUCAST) (2013) guidelines. A total of 4047 pathogenic strains were isolated from 18 tertiary hospitals in 18 cities across China between July 2011 and June 2012. MIC results indicated that the vast majority of *Enterobacteriaceae* maintained high susceptibility to doripenem, with a lower resistance rate (1.9%) than that observed for other drugs tested. In the case of non-fermenting Gram-negative isolates, the resistance rate of *Pseudomonas aeruginosa* was 16.2%, which was less than that of imipenem and meropenem, and the *Acinetobacter baumannii* doripenem resistance rate was 67.4%. Doripenem also showed good *in vitro* activity against other the bacteria tested. This study suggests that the gradual increase in carbapenem nonsusceptible *Enterobacteriaceae* should be monitored carefully alongside the increasing multidrug-resistant and extensively drug-resistant *A. baumannii*.

The Journal of Antibiotics (2015) 68, 496–500; doi:10.1038/ja.2015.25; published online 8 April 2015

INTRODUCTION

Carbapenems are a first choice treatment against serious bacterial infections due to their broad specificity and potent activity.¹ Doripenem (S-4661) is a carbapenem developed by Shionogi and approved for marketing in Japan in September 2005.² This drug has broad-spectrum activity against Gram-positive cocci and Gram-negative bacteria and anaerobes, and is stable against extended-spectrum β -lactamases, AmpC β -lactamases and dehydropeptidase-I. The post-antibiotic effect (PAE) of doripenem against *Pseudomonas aeruginosa* is ~2 h *in vitro*, and MIC values are 2–4-fold less than that observed for imipenem and meropenem. Pharmacokinetic parameters are similar to meropenem, with a bound-drug concentration in plasma of 8.9%.^{3,4} In October 2007, the US Food and Drug Administration (FDA) approved doripenem as a new drug to treat complicated urinary tract and intra-abdominal infections.⁵ The purpose of this study was to evaluate the *in vitro* activity of doripenem against a collection of pathogens isolated from tertiary hospitals in China.

MATERIALS AND METHODS

Bacterial strains

A total of 4047 strains were isolated from 18 tertiary hospitals in 18 cities across China between July 2011 and June 2012; *Escherichia coli* ATCC25922, *E. coli* ATCC35218, *P. aeruginosa* ATCC27853, *Haemophilus influenzae* ATCC49247, *Staphylococcus aureus* ATCC29213 and *Streptococcus pneumoniae* ATCC49619 was used as the control strain.

Antimicrobials

Doripenem and moxalactam were provided by Shionogi. Penicillin, oxacillin, ampicillin, piperacillin, meropenem, tazobactam, gentamicin and minocyclin were purchased from the National Institute for the Control of Pharmaceutical and Biological Products of China. Colistin and chloramphenicol were purchased from Sigma (Shanghai, China). Cefotaxime and cefoperazone were provided by China Nanjing Youke Biomedical Co. (Nanjing, China). Ceftazidime was provided by China Shenzhen Jiuxin Pharma Co., and cefepime was purchased from Bristol-Myers Squibb (Shanghai, China). Cefoxitin was provided by China Haikou Pharma Co, imipenem was purchased from Merck (Elkton, VA, USA), and sulbactam and Azithromycin were from Pfizer (Dalian, China). Levofloxacin was obtained from Daiichi-Sankyo Co, sulfamethoxazole and trimethoprim were from China Shandong Xinda Pharma Co, and vancomycin was purchased from Eli Lilly (Kobe, Japan).

Susceptibility test

MICs were performed using the agar dilution method recommended by the Clinical Laboratory Standards Institute (CLSI) central laboratory.

MIC assays

Susceptibility of isolates to antimicrobial agents was determined using CLSI (2014). The U.S. FDA susceptibility criteria of doripenem (in doripenem package insert) were used same time to *Enterobacteriaceae* and *Acinetobacter baumannii* because these differ from CLSI.

Table 1 Antibacterial activity ($\mu\text{g ml}^{-1}$) of antimicrobial agents against *E. coli*

Agents	<i>E. coli</i> (600)				ESBLs ⁻ <i>E. coli</i> (184)				ESBLs ⁺ <i>E. coli</i> (416)			
	MIC ₅₀	MIC ₉₀	S %	R %	MIC ₅₀	MIC ₉₀	S %	R %	MIC ₅₀	MIC ₉₀	S %	R %
Doripenem	0.01	0.03	99.5	0.3	0.01	0.03	98.9	1.1	0.01	0.03	99.8	0.0
Doripenem ^a	—	—	99.2	0.8	—	—	97.8	2.2	—	—	99.8	0.2
Imipenem	0.13	0.25	98.8	0.3	0.13	0.25	97.8	1.1	0.13	0.25	99.3	0.0
Meropenem	0.01	0.06	99.3	0.3	0.01	0.03	97.8	1.1	0.01	0.06	100.0	0.0
Ampicillin	> 256	> 256	6.0	93.8	> 256	> 256	19.6	79.9	> 256	> 256	0.0	100.0
Cefotaxime	32	> 256	26.7	73.0	0.06	16	86.4	13.6	64	> 256	0.2	99.3
Ceftazidime	2	64	55.7	36.8	0.13	32	85.3	14.1	8	64	42.5	46.9
Cefepime	4	32	41.7	27.5	0.03	1	91.8	5.4	8	64	19.5	37.3
Moxalactam	0.25	2	95.7	1.3	0.13	4	92.4	2.2	0.5	2	97.1	1.0
TZP ^b	8	32	85.7	3.0	4	32	87.5	4.3	8	32	84.9	2.4
CSL ^c	8	32	80.7	9.0	0.5	16	92.9	3.3	16	64	75.2	11.5
Gentamicin	32	128	38.5	59.8	16	128	46.2	52.7	32	128	35.1	63.0
Minocyclin	4	32	63.2	26.0	2	32	67.9	21.2	4	32	61.1	28.1
Levofloxacin	8	32	34.2	58.0	1	16	52.2	37.0	8	32	26.2	67.3

Abbreviations: R, resistance; S, susceptibility.

^aAccording to the US FDA criteria (S: $\leq 0.5 \mu\text{g ml}^{-1}$; nonsusceptible: $> 0.5 \mu\text{g ml}^{-1}$).^bPiperacillin/tazobactam (8:1).^cCefoperazone/sulbactam (2:1). The breakpoint of cefoperazone was used for CSL (S: $\leq 16 \mu\text{g ml}^{-1}$; R: $\geq 64 \mu\text{g ml}^{-1}$).**Table 2** Antibacterial activity ($\mu\text{g ml}^{-1}$) of antimicrobial agents against *K. pneumoniae*

Agents	<i>K. pneumoniae</i> (500)				ESBLs ⁻ <i>K. pneumoniae</i> (279)				ESBLs ⁺ <i>K. pneumoniae</i> (221)			
	MIC ₅₀	MIC ₉₀	S %	R %	MIC ₅₀	MIC ₉₀	S %	R %	MIC ₅₀	MIC ₉₀	S %	R %
Doripenem	0.03	0.06	95.8	3.4	0.03	0.13	92.5	6.1	0.03	0.06	100.0	0.0
Doripenem ^a	—	—	95.2	4.8	—	—	91.8	8.2	—	—	99.5	0.5
Imipenem	0.13	0.25	95.8	3.6	0.25	0.5	92.8	6.5	0.13	0.25	99.5	0.0
Meropenem	0.03	0.06	95.6	3.6	0.03	0.25	92.1	6.5	0.03	0.06	100.0	0.0
Cefotaxime	4	256	48.0	50.2	0.03	32	84.9	12.9	64	256	1.4	97.3
Ceftazidime	1	128	65.4	28.8	0.13	32	85.7	12.2	8	128	39.8	49.8
Cefepime	0.5	32	62.4	23.4	0.03	4	89.6	9.0	8	64	28.1	41.6
Moxalactam	0.25	4	93.8	4.2	0.13	8	90.0	6.8	0.5	2	98.6	0.9
TZP ^b	8	64	77.6	8.6	4	128	85.7	11.1	16	64	67.4	5.4
CSL ^c	4	64	74.4	12.6	0.25	64	86.7	10.8	16	64	58.8	14.9
Gentamicin	0.5	128	62.4	36.6	0.5	32	86.7	12.2	32	> 256	31.7	67.4
Minocyclin	2	32	67.0	25.2	2	16	82.4	10.8	8	64	47.5	43.4
Levofloxacin	0.25	32	74.2	23.4	0.06	8	87.5	11.1	1	64	57.5	38.9

Abbreviations: R, resistance; S, susceptibility.

^aAccording to the US FDA criteria (S: $\leq 0.5 \mu\text{g ml}^{-1}$; nonsusceptible: $> 0.5 \mu\text{g ml}^{-1}$).^bPiperacillin/tazobactam (8:1).^cCefoperazone/sulbactam (2:1). The breakpoint of cefoperazone was used for CSL (S: $\leq 16 \mu\text{g ml}^{-1}$; R: $\geq 64 \mu\text{g ml}^{-1}$).

RESULTS

Antibacterial activity of doripenem and other antimicrobial agents against *Enterobacteriaceae*

The detection rates of extended-spectrum beta-lactamase (ESBL)-producing *E. coli* and *Klebsiella pneumoniae* were 69.3% and 44.2%, respectively (Tables 1 and 2). Doripenem showed potent *in vitro* activity against *Enterobacteriaceae*. The susceptibility for doripenem against all *Enterobacteriaceae* isolates was $> 95\%$ ($\text{MIC}_{90} \leq 0.25 \mu\text{g ml}^{-1}$ for different genera). Carbapenems are important *Enterobacteriaceae* infection treatments, and this was reflected in the resistance rates for doripenem, meropenem and imipenem of 1.9%, 2.0% and 2.3%, respectively. The antimicrobial activity of doripenem was similar to meropenem, and slightly higher than imipenem (Tables 1–3). In addition, moxalactam, piperacillin/tazobactam and cefoperazone/sulbactam exhibited a strong activity against *Enterobacteriaceae* isolates.

Carbapenem followed by moxalactam showed the highest antibacterial activity against ESBL-positive *E. coli* and *K. pneumoniae*.

Antibacterial activity of doripenem and other antimicrobial agents against non-fermenting Gram-negative bacteria

Rates of resistance for most antimicrobial agents against *P. aeruginosa* ranged from 10 to 30% (Tables 4 and 5), and was 16.2% for doripenem, lower than for meropenem and imipenem. The susceptibility of imipenem-susceptible and imipenem-resistant *P. aeruginosa* to doripenem was 99.5 and 39.9%, respectively, and partial cross-resistance occurred in some cases, suggesting doripenem remained effective against some imipenem-resistant *P. aeruginosa*. Additionally, ceftazidime and cefepime were also effective against

Table 3 Antibacterial activity ($\mu\text{g ml}^{-1}$) of antimicrobial agents against other *Enterobacteriaceae*

Agents	<i>E. cloacae</i> (153)				<i>E. aerogenes</i> (97)				<i>Citrobacter sp.</i> (88)				<i>Serratia sp.</i> (102)				<i>Proteus sp.</i> (100)			
	MIC ₅₀	MIC ₉₀	S %	R %	MIC ₅₀	MIC ₉₀	S %	R %	MIC ₅₀	MIC ₉₀	S %	R %	MIC ₅₀	MIC ₉₀	S %	R %	MIC ₅₀	MIC ₉₀	S %	R %
Doripenem	0.03	0.13	97.4	2.0	0.03	0.06	95.9	4.1	0.03	0.06	97.7	1.1	0.06	0.13	96.1	3.9	0.06	0.13	100.0	0.0
Doripenem ^a	—	—	95.4	4.6	—	—	93.8	6.2	—	—	97.7	2.3	—	—	96.1	3.9	—	—	100.0	0.0
Imipenem	0.25	0.25	96.1	2.6	0.25	0.5	93.8	5.2	0.13	0.25	96.6	2.3	0.25	0.5	95.1	4.9	0.5	1	93.0	2.0
Meropenem	0.03	0.13	96.7	2.6	0.03	0.06	94.8	3.1	0.03	0.06	97.7	2.3	0.03	0.06	96.1	3.9	0.03	0.13	100.0	0.0
Cefotaxime	16	256	45.8	53.6	1	256	54.6	43.3	2	128	50.0	48.9	0.5	64	75.5	21.6	0.03	16	70.0	28.0
Ceftazidime	4	256	52.3	41.2	1	128	61.9	35.1	0.5	64	63.6	30.7	0.25	8	89.2	7.8	0.06	0.25	92.0	8.0
Cefepime	0.25	16	67.3	18.3	0.13	16	81.4	15.5	0.06	8	85.2	5.7	0.13	8	85.3	7.8	0.06	8	80.0	9.0
Moxalactam	0.25	32	83.0	6.5	0.25	8	90.7	6.2	0.25	16	85.2	6.8	0.25	2	95.1	0.0	0.13	0.5	100.0	0.0
TZP ^b	8	64	68.0	9.8	8	64	72.2	4.1	3	64	71.6	8.0	2	16	92.2	2.9	1	4	99.0	0.0
CSL ^c	4	64	75.8	13.7	1	32	86.6	9.3	1	32	83.0	8.0	2	16	91.2	4.9	1	4	98.0	0.0
Gentamicin	0.5	128	72.5	26.8	0.5	8	89.7	9.3	0.5	64	70.5	28.4	0.5	64	81.4	18.6	1	128	75.0	23.0
Minocyclin	2	64	73.2	22.9	4	32	64.9	15.5	4	16	70.5	20.5	4	8	87.3	3.9	32	64	6.0	79.0
Levofloxacin	0.13	8	79.7	14.4	0.06	4	85.6	6.2	0.25	4	86.4	8.0	0.25	2	90.2	6.9	1	16	65.0	30.0

Abbreviations: R, resistance; S, susceptibility.

^aAccording to US FDA criteria (S: $\leq 0.5 \mu\text{g ml}^{-1}$; nonsusceptible: $> 0.5 \mu\text{g ml}^{-1}$).^bPiperacillin/tazobactam (8:1).^cCefoperazone/sulbactam (2:1). The breakpoint of cefoperazone was used for CSL (S: $\leq 16 \mu\text{g ml}^{-1}$; R: $\geq 64 \mu\text{g ml}^{-1}$).**Table 4** Antibacterial activity ($\mu\text{g ml}^{-1}$) of antimicrobial agents against *P. aeruginosa*

Agents	<i>P. aeruginosa</i> (610)				IMP-S <i>P. aeruginosa</i> (367) ^a				IMP-NS <i>P. aeruginosa</i> (243) ^b			
	MIC ₅₀	MIC ₉₀	S%	R%	MIC ₅₀	MIC ₉₀	S%	R%	MIC ₅₀	MIC ₉₀	S%	R%
Doripenem	0.5	8	73.8	16.2	0.25	1	99.5	0.5	4	32	35.0	39.9
Imipenem	2	16	60.2	31.3	2	2	100.0	0.0	16	32	0.0	78.6
Meropenem	0.5	16	68.2	24.4	0.25	1	97.5	0.8	8	32	23.9	60.1
Ceftazidime	2	64	75.9	18.5	2	16	87.7	8.4	8	> 256	58.0	33.7
Cefepime	2	32	76.7	12.0	2	8	91.6	3.5	8	128	54.3	24.7
Moxalactam ^c	32	128	17.0	36.7	16	64	21.0	21.8	64	256	11.1	59.3
TZP ^d	8	128	68.9	10.3	4	64	82.6	4.4	32	128	48.1	19.3
CSL ^e	8	128	66.7	21.5	8	32	82.6	7.6	32	128	42.8	42.4
Gentamicin	2	> 256	72.1	25.1	2	> 256	83.1	14.2	4	> 256	55.6	41.6
Levofloxacin	1	16	65.7	26.1	0.5	8	82.3	12.5	4	64	40.7	46.5

^aIMP-S: Imipenem-susceptibility.^bIMP-NS: Imipenem -nonsusceptibility.^cThe breakpoint of moxalactam against *Enterobacteriaceae* was used here (S: $\leq 8 \mu\text{g ml}^{-1}$; R: $\geq 64 \mu\text{g ml}^{-1}$).^dPiperacillin/tazobactam (8:1).^eCefoperazone/sulbactam (2:1). The breakpoint of cefoperazone against *Enterobacteriaceae* was used for CSL (S: $\leq 16 \mu\text{g ml}^{-1}$; R: $\geq 64 \mu\text{g ml}^{-1}$).

imipenem-susceptible *P. aeruginosa*, but moxalactam was not very active against *P. aeruginosa*.

The resistance rates for *A. baumannii* against most antimicrobial agents ranged from 60 to 80%, and the resistance to doripenem was 67.4%, which was comparable to meropenem and imipenem. The rates of susceptibility and resistance of imipenem-susceptible *A. baumannii* to doripenem were 95.9% and 0.5%, respectively. Neither doripenem nor meropenem were active against imipenem-nonsusceptible strains. The susceptibility to colistin was 96.6%, which was the most active antibacterial agent against this species.

Antibacterial activity of doripenem and other antimicrobial agents against Gram-positive bacteria

The susceptibility of methicillin-resistant *S. aureus* and methicillin-resistant *S. epidermidis* to doripenem were 45.4% and 81.6%, respectively (Tables 6 and 7). The revised CLSI (2014) guidelines

eliminated breakpoints (interpretive criteria) for all β -lactams except oxacillin, cefoxitin and penicillin, and included breakpoints for ceftaroline (a cephalosporin with anti-methicillin-resistant *S. aureus* activity). We did not calculate the rates of susceptibility or resistance for antibacterial agents for which the breakpoint data were not included in these guidelines.

The MIC₉₀ values for doripenem against methicillin-sensitive *Staphylococcus sp.* were $< 0.5 \mu\text{g ml}^{-1}$, which demonstrated the effectiveness of doripenem against these strains. Similar findings were observed for imipenem and meropenem. All other agents except penicillin and azithromycin showed a strong activity against methicillin-sensitive *Staphylococcus sp.*, and vancomycin resistance was not observed in *staphylococci*. No β -lactam antimicrobial drugs, even when active *in vitro*, were active against methicillin-resistant *S. aureus* in clinical treatments, suggesting that the isolated strains could be classified as resistant.

Table 5 Antibacterial activity ($\mu\text{g ml}^{-1}$) of antimicrobial agents against *A. baumannii*

	<i>A. baumannii</i> (594)				IMP-S <i>A. baumannii</i> (194) ^a				IMP-NS <i>A. baumannii</i> (400) ^b			
	MIC ₅₀	MIC ₉₀	S %	R %	MIC ₅₀	MIC ₉₀	S %	R %	MIC ₅₀	MIC ₉₀	S %	R %
Doripenem	32	64	31.3	67.4	0.25	2	95.9	0.5	32	64	0.0	99.7
Doripenem ^c	—	—	27.8	72.2	—	—	85.1	14.9	—	—	0.0	100.0
Imepenem	32	64	32.7	66.3	0.25	2	100.0	0.0	32	64	0.0	98.5
Meropenem	32	128	29.6	68.0	0.5	4	90.7	2.6	64	128	0.0	99.7
SAM ^d	64	128	22.6	73.6	2	32	69.1	24.7	64	128	0.0	97.2
Cefotaxime	> 256	> 256	12.8	75.1	16	> 256	38.1	28.9	> 256	> 256	0.5	97.5
Ceftazidime	64	> 256	25.3	74.1	4	128	71.1	27.9	128	> 256	3.0	96.5
Cefepime	32	256	25.4	62.8	2	32	75.3	11.8	64	256	1.3	87.5
Moxalactam ^e	128	256	1.5	82.7	32	128	4.6	48.5	128	256	0.0	99.2
TZP ^f	128	> 256	22.6	67.5	16	64	68.6	7.2	256	> 256	0.3	96.7
CSL ^g	32	128	28.6	49.2	2	32	76.8	9.3	64	128	5.3	68.5
Gentamicin	> 256	> 256	24.2	75.4	1	> 256	66.0	33.5	> 256	> 256	4.0	95.7
Minocyclin	4	16	58.4	22.7	0.25	8	87.6	7.2	8	32	44.3	30.2
Levofloxacin	8	16	25.3	54.7	0.13	8	71.6	19.6	8	16	2.8	71.7
Colistin	1	2	96.6	3.4	1	2	95.9	4.1	1	1	97.0	3.0

^aIMP-S: Imipenem-susceptibility.^bIMP-NS: Imipenem -nonsusceptibility.^cAccording to the US FDA criteria (S: $\leq 1 \mu\text{g ml}^{-1}$; Nonsusceptible: $> 1 \mu\text{g ml}^{-1}$).^dAmpicillin/sulbactam (2:1).^eThe breakpoint of moxalactam against *Enterobacteriaceae* was used here (S: $\leq 8 \mu\text{g ml}^{-1}$; R: $\geq 64 \mu\text{g ml}^{-1}$).^fPiperacillin/tazobactam (8:1).^gCefoperazone/sulbactam (2:1). The breakpoint of cefoperazone against *Enterobacteriaceae* was used for CSL (S: $\leq 16 \text{ mg/l}$; R: $\geq 64 \text{ mg/l}$).**Table 6** Antibacterial activity ($\mu\text{g ml}^{-1}$) of antimicrobial agents against *S. aureus* and *S. epidermidis*

Agents	<i>S. aureus</i> (601)				MSSA (328)				<i>S. epidermidis</i> (98)				MSSE (18)			
	MIC ₅₀	MIC ₉₀	S %	R %	MIC ₅₀	MIC ₉₀	S %	R %	MIC ₅₀	MIC ₉₀	S %	R %	MIC ₅₀	MIC ₉₀	S %	R %
Doripenem	0.06	32	—	—	0.03	0.06	—	—	0.25	2	—	—	0.03	0.5	—	—
Imepenem	0.03	64	—	—	0.03	0.03	—	—	0.13	0.5	—	—	0.01	0.25	—	—
Meropenem	0.25	32	—	—	0.13	0.25	—	—	0.5	2	—	—	0.06	2	—	—
Penicillin	1	64	9.5	90.5	0.5	1	16.2	83.8	1	8	14.3	85.7	0.13	0.5	55.6	44.4
Oxacillin	0.5	256	57.4	42.6	0.25	0.5	100.0	0.0	1	32	18.4	81.6	0.13	0.25	100.0	0.0
Cefoxitin	4	256	55.1	44.9	2	4	100.0	0.0	8	32	—	—	2	4	—	—
Moxalactam	16	> 256	—	—	8	16	—	—	32	256	—	—	16	256	—	—
TZP ^a	4	128	—	—	2	4	—	—	2	4	—	—	0.5	2	—	—
Gentamicin	0.25	64	53.6	41.9	0.25	16	79.9	14.3	0.25	32	70.4	18.4	0.13	16	88.9	11.1
Azithromycin	> 256	> 256	23.8	74.5	> 256	> 256	32.0	68.0	64	> 256	17.3	81.6	64	> 256	38.9	61.1
Minocyclin	0.06	2	97.8	0.7	0.06	0.13	100.0	0.0	0.13	0.5	100.0	0.0	0.06	0.25	100.0	0.0
Levofloxacin	0.25	64	56.2	43.1	0.25	4	87.8	11.3	2	8	45.9	38.8	0.13	4	72.2	22.2
Vancomycin	0.5	1	100.0	0.0	0.5	1	100.0	0.0	1	2	100.0	0.0	1	1	100.0	0.0

—: No breakpoint.

^aPiperacillin/tazobactam (8:1).

The rates of resistance and intermediate resistance of penicillin against *S. pneumoniae* strains (not including meningitis isolates) were 1.5% and 7.8%, respectively. Susceptibility to doripenem was 91.9%, which was significantly higher than imipenem and meropenem. Penicillin, levofloxacin and vancomycin also showed good activity against *S. pneumoniae*. *Streptococcus pyogenes* isolates were also susceptible to most antimicrobial agents tested except azithromycin (resistance rate=92.3%), and the susceptibility for doripenem was 100% (MIC $\leq 0.06 \mu\text{g ml}^{-1}$). Other β -hemolytic isolates were also susceptible to most antimicrobial agents, and the susceptibility to doripenem equaled to meropenem in 98.1% of cases. The susceptibility of viridans isolates to doripenem was 92.7%, which was higher than that for all other agents tested except vancomycin.

DISCUSSION

The results of this extensive study confirmed that doripenem maintained strong antibacterial activity against *Enterobacteriaceae*, with a resistance of just 1.9%, which was lower than all other carbapenems tested. The mean resistance rate of *K. pneumoniae* isolates toward carbapenems ranged from 3.4 to 3.6%. These strains are known to produce carbapenemases or other β -lactamases that are present in ESBL-negative groups but are not inhibited by clavulanic acid. Resistance to carbapenems was therefore higher in ESBL-negative bacilli than in ESBL-producing strains. It is worth noting that increasing resistance against carbapenems has emerged in *K. pneumoniae*.⁶ Compared with imipenem and meropenem, doripenem (resistance=16.2%) was more active against *P. aeruginosa*.

Table 7 Antibacterial activity ($\mu\text{g ml}^{-1}$) of antimicrobial agents against *Streptococcus* sp.

Agents	<i>S. pneumoniae</i> (344)				<i>S. pyogenes</i> (52)				β -Hemolytic group except <i>S. pyogenes</i> (53)				Viridans group (55)			
	MIC ₅₀	MIC ₉₀	S %	R %	MIC ₅₀	MIC ₉₀	S %	R %	MIC ₅₀	MIC ₉₀	S %	R %	MIC ₅₀	MIC ₉₀	S %	R %
Doripenem	0.5	1	91.9	8.1 ^a	0.01	0.01	100.0	—	0.01	0.03	98.1	1.9 ^a	0.06	1	92.7	7.3 ^a
Imepenem	0.13	0.5	51.2	2.6	0.01	0.01	—	—	0.01	0.03	—	—	0.06	2	—	—
Meropenem	0.5	1	48.5	23.0	0.01	0.01	100.0	—	0.03	0.06	98.1	1.9 ^a	0.13	2	85.5	14.5 ^a
Penicillin ^b	1	2	90.7	1.5	0.01	0.01	98.1	1.9 ^a	0.03	0.13	90.6	9.4 ^a	0.03	4	56.4	14.5
Ampicillin	2	8	—	—	0.01	0.01	98.1	1.9 ^a	0.13	0.13	98.1	1.9 ^a	0.5	116	45.5	16.4
Cefotaxime	1	4	53.8	22.1	0.01	0.03	100.0	—	0.06	0.13	98.1	1.9 ^a	0.25	8	74.5	25.5 ^a
Cefepime	2	4	45.6	14.0	0.01	0.03	100.0	—	0.03	0.5	92.5	7.5 ^a	0.13	4	83.6	16.4 ^a
Moxalactam	32	64	—	—	0.5	4	—	—	4	16	—	—	32	128	—	—
TZP ^c	2	8	—	—	0.03	0.13	—	—	0.25	0.25	—	—	0.25	16	—	—
Azithromycin	>256	>256	0.3	98.0	>256	>256	7.7	92.3	128	>256	18.9	75.5	64	>256	32.7	67.3
Minocyclin	8	16	—	—	4	16	—	—	8	32	—	—	2	16	—	—
Levofloxacin	1	2	97.4	1.2	0.25	0.5	100.0	0.0	0.5	32	75.5	22.6	0.5	32	69.1	30.9
Vancomycin	0.5	0.5	100.0	—	0.25	0.5	100.0	—	0.5	1	98.1	1.9 ^a	0.25	0.5	100.0	—

—: No breakpoint.

^aNon-susceptibility rate.^bNonmeningitis breakpoint.^cPiperacillin/tazobactam (8:1).

Carbapenem-resistance has also increased in *A. baumannii*, from 1% in 2000–2001 to >60% more recently.^{6–11} Multidrug-resistant *A. baumannii* is a particular concern, and can account for 80.3% of strains.¹¹ The doripenem activity against *Enterobacteriaceae* (MIC₉₀ \leq 0.25 $\mu\text{g ml}^{-1}$ for different genus) and *P. aeruginosa* (MIC₉₀ 8 $\mu\text{g ml}^{-1}$) determined in this study are in agreement with previously published international reports (MIC₉₀ = 0.06–0.5 $\mu\text{g ml}^{-1}$ for *Enterobacteriaceae* and MIC₉₀ = 1–16 $\mu\text{g ml}^{-1}$ for *P. aeruginosa*).^{12,13} However, our data for *A. baumannii*, differed from the published Surveillance of Multicentre Antimicrobial Resistance in Taiwan (SMART) surveillance data.¹² *A. baumannii* susceptibility to doripenem was 31.3% in this study, which was much lower than the SMART surveillance figure of 79%. Similarly, MIC₉₀ values were 64 and 16 $\mu\text{g ml}^{-1}$ in the current study and SMART surveillance report.¹² These differences may be due to different criteria studied, since we used \leq 2 $\mu\text{g ml}^{-1}$ as the susceptible breakpoint for doripenem against *A. baumannii* based on the CLSI 2014 report, whereas the SMART surveillance report used \leq 4 $\mu\text{g ml}^{-1}$. In addition, specimen collection times were different: we collected strains between July 2011 and June 2012, whereas the SMART surveillance collected the specimens between September and November 2005. Differences in the geographical area where organisms were collected is another potential source of inconsistency: our strains were collected from mainland China, whereas the SMART surveillance samples were isolated in Taiwan. These factors may all contribute to the differences observed. As stated above, carbapenem-resistant *A. baumannii* have increased dramatically during the past decade, and therefore have a higher MIC than in the past. Using a lower susceptibility breakpoint will therefore result in a lower rate of susceptibility.

ACKNOWLEDGEMENTS

The following hospitals contributed to this study: (1) the Institute of Clinical Pharmacology, Peking University First Hospital, Beijing; (2) the Beijing Hospital, Beijing; (3) the Ji Lin University Second Hospital, Changchun; (4) the Tianjin Medical University General Hospital, Tianjin; (5) the Second Hospital of Hebei Medical University, Shijiazhuang; (6) the First Affiliated Hospital with Nanjing Medical University, Nanjing; (7) the Zhongshan Hospital Fudan

University, Shanghai; (8) Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou; (9) Guangzhou Women and Children's Medical Center, Guangzhou; (10) Renmin Hospital of Wuhan University, Wuhan; (11) Xiangya Hospital Central-South University, Changsha; (12) Kunming First People's Hospital, Kunming; (13) the Affiliated Hospital of Guiyang Medical College, Guiyang; (14) Southwest Hospital, Third Military Medical University, Chongqing; (15) Xijing Hospital, Forth Military Medical University, Xi'an; (16) Jinan Central Hospital Affiliated to Shandong University, Jinan; (17) the Lanzhou University Second Hospital, Lanzhou; (18) the First Teaching Hospital of Xinjiang Medical University, Wu lu mu qi; (19) the Hanzhong Center Hospital, Hanzhong.

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