

# In-Vitro Activity of Doripenem vs. Imipenem & Meropenem against Clinical Isolates of Pseudomonas and Other Oxidase-Positive Gram-Negative Bacilli

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## ABSTRACT

**Background & objectives:** Doripenem is approved by United States Food and Drug Administration (US FDA) for the treatment of complicated urinary tract infections (cUTI), complicated intra-abdominal infections (cIAI) and in Europe for ventilator-associated pneumonia (VAP). We attempted to compare the *in vitro* activity of doripenem with imipenem and meropenem using current CLSI guidelines among clinical isolates of *Pseudomonas spp.* and other oxidase positive Gram-negative bacilli from clinical samples.

**Methods:** Eighty consecutive clinical isolates were included in the study. Samples included were pus (n=29), blood (n=7), urine (n=24) and 20 sputum (n=20). MIC values of the imipenem, meropenem and doripenem were determined by E tests. Out of 72 Polymyxin B sensitive isolates 34 were *Pseudomonas aeruginosa*, 30 Fluorescent group and 8 *Alcaligenes* group. Polymyxin B (n=8) resistant isolates were identified as *Burkholderia* group. *Pseudomonas aeruginosa* ATCC 29853 was used as quality control strain.

**Results:** In the Polymyxin B sensitive group (n=72), 29.1%, 23.6% and 26.3% isolates were susceptible to imipenem, meropenem and doripenem respectively. In the Polymyxin B resistant group (n=8) only one isolate was sensitive to imipenem and meropenem while 5 were moderately sensitive to doripenem.

**Interpretation & conclusions:** Among Polymyxin B sensitive isolates meropenem was found least susceptible as compared to doripenem and imipenem. Doripenem may be a valuable alternative in Polymyxin B resistant isolates for the treatment of serious infections and in the intensive care unit where patients have predisposing conditions for seizures.

**Keywords:** Doripenem, meropenem, imipenem, E test, *Pseudomonas*, Non-fermenting gram negative bacilli

## INTRODUCTION

The synthesis of new carbapenem remains an area of intense research because of the broad spectrum antibacterial activity of this chemical class. <sup>(1-3)</sup> Doripenem is a recently released antibiotic with significant potential for use in *Pseudomonas aeruginosa* infections occur in CF and burn patients. <sup>(4)</sup> Non-fermenting Gram negative

bacilli (NFGNB) have emerged as important multi-drug resistant nosocomial pathogens and may be associated with poor clinical outcomes. <sup>(5)</sup> Doripenem is widely being used for the treatment of complicated urinary tract infections (cUTIs) and complicated intra-abdominal infections (cIAIs) caused by these organisms. <sup>(6)</sup> The In-vitro antimicrobial activity of doripenem

is generally comparable to that of meropenem and imipenem. <sup>(7)</sup> The activity of doripenem against *P. aeruginosa* isolates is slightly better than that of other carbapenems. However, development of carbapenem resistance may significantly compromise their efficacy. <sup>(8)</sup> Resistance to carbapenems including doripenem resulted from the complex interaction of several mechanisms including loss of the OprDporin, over-expression of efflux systems (MexAB-OprM, MexEF-OprN) and production of carbapenemase activity, usually a metallo- $\beta$ -lactamase (MBL). <sup>(9-12)</sup> Doripenem as a new carbapenem offers potentially enhanced carbapenem activity but does not expand the spectrum of activity of this class. There are however few studies on the reliability of testing doripenem against oxidase positive NFGNB by the KBDD method.

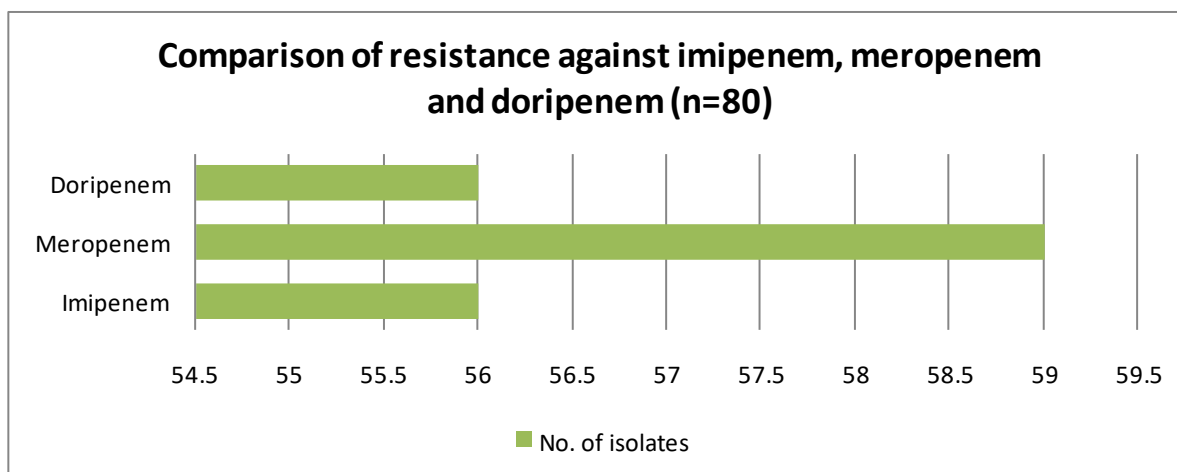
Since, *P. aeruginosa* is one of the most frequently isolated clinical pathogens, we designed the study to determine the susceptibility patterns of all the isolates and to compare the in-vitro antibacterial activity of doripenem with that of imipenem and meropenem among the isolates of *Pseudomonas* and other oxidase-positive gram-negative bacilli.

## METHODS

From January to March 2014, a total of 80 non-repetitive clinical *Pseudomonas* spp. and oxidase positive NFGNB isolates recovered from urine, sputum, blood and pus samples of patients with cUTIs and cIAIs were included in this study. Among 80 isolates 72 isolates were tested polymyxin B sensitive and 8 as polymyxin B resistant by Kirby Bauer Disc Diffusion methodology. Polymyxin B sensitive isolates were identified by routine biochemical tests as *Pseudomonas aeruginosa* (n=34), Fluorescent group (n=30), and Alcaligenes group (n=8) where as polymyxin B resistant isolates were identified as *Burkholderia cepacia* complex (n=8) by standard bacteriological tests. MIC values of the imipenem, meropenem and doripenem were determined by E-tests. Results were interpreted according to Clinical and Laboratory Standards Institute (CLSI) criteria, where applicable. <sup>(13)</sup> FDA interpretive criteria were applied to doripenem results (susceptible  $\leq 2\text{mg/l}$  for *P. aeruginosa*). <sup>(14)</sup> The results were examined to ensure that reported MICs were within acceptable standards set by CLSI based on a comparator agent and the following ATCC quality control strain, *Pseudomonas aeruginosa* ATCC 29853.

## RESULTS AND DISCUSSION

The susceptibility pattern of 80 isolates against doripenem, imipenem and meropenem using E-test is summarized in Table 1.



**Table 1.** Susceptibility pattern of imipenem, meropenem & doripenem by Etest (n=80) against polymyxin B sensitive & resistant isolates

	Susceptibility of no. of isolates considering MIC values									
	Imipenem			Meropenem			Doripenem			
	S	I	R	S	I	R	S	I	R	
PB Sensitive	<i>Pseudomonas aeruginosa</i>	13	0	21	10	2	22	12	0	22
	Fluorescent group	3	2	25	2	2	26	4	0	26
	Alcaligenes group	4	0	4	4	0	4	3	0	5
PB Resistant	Burkholderia group	1	1	6	1	0	7	0	5	3

The In-vitro antimicrobial activity of doripenem is generally comparable to that of meropenem and imipenem. (7) Infections caused by *P. aeruginosa* in burn and CF patients often treated with difficulty due to the emergence of resistance and lack of effective antibiotics. (15) Doripenem as a new carbapenem offers potentially enhanced carbapenem activity but does not expand the spectrum of activity of this class. (4) Like other carbapenems, doripenem has stability against many  $\beta$ -lactamases, but remains labile to class B enzymes, known as metallo- $\beta$ -lactamases. (7) Therefore, in the present work, we attempted to assess the in-vitro activity of doripenem vs. imipenem and meropenem against clinical isolates of *Pseudomonas* and other oxidase-positive gram-negative bacilli. Among the total 80 isolates included in the study, we found 56 isolates resistant to both doripenem and imipenem while 59 isolates were resistant to meropenem. So, 3 isolates were additionally meropenem resistant were susceptible to imipenem but were resistant to doripenem. The susceptibility pattern of imipenem, meropenem and doripenem by Etest against polymyxin B sensitive and resistant isolates showed 13 isolates that were susceptible to imipenem for *Pseudomonas aeruginosa* than doripenem and meropenem. Among fluorescent less susceptible isolates were identified for meropenem and imipenem than doripenem whereas among *Burkholderia* only 1 susceptible isolate was identified for both imipenem and meropenem and none for doripenem. *Alcaligenes* group also showed similar susceptibility to both imipenem and meropenem than doripenem, which was less susceptible. So, from the data it seems that doripenem and imipenem both can be considered as the potent carbapenems

against *Pseudomonas aeruginosa* for no much discrepancy observed among them.

The Clinical Laboratory Standards Institute (CLSI) guidelines do not provide interpretive break-points of doripenem for oxidase positive NFGNB other than *Pseudomonas aeruginosa* while the European Committee for Antimicrobial Susceptibility Testing (EUCAST) has clubbed all isolates under the heading *Pseudomonas* spp.

## CONCLUSION

Although in previous studies doripenem was found more active than imipenem and meropenem against *P. aeruginosa* isolated from clinical patients, no much superiority of doripenem is observed to old carbapenems in clinical isolates of *Pseudomonas* spp. and oxidase positive NFGNB isolates recovered from urine, sputum, blood and pus samples of patients with cUTIs and cIAIs. Doripenem still may be a valuable alternative in Polymyxin B resistant isolates for the treatment of serious infections and in the intensive care unit where patients have predisposing conditions for seizures. In terms of MIC level of imipenem, this antibiotic is the most active but this advantage is not partly offset by higher regulatory breakpoints. Meropenem is the least potent agent against for *P. aeruginosa* and other fluorescent groups and NFGNB. The limitation of this study is that the E test was used as the reference method for MIC determination and we tested only a small number of isolates.

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**Competing interests:** None declared

**Ethical approval:** Not required

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