

# Activity of Doripenem and Other Carbapenems Against 18,538 Pathogens Isolated from Canadian Hospitals: CANWARD 2007-2009

G. G. ZHANEL, M. DeCORBY, N. LAING, P. SIMMER, F. TAILOR, H. ADAM, J. A. KARLOWSKY, P. LAGACE-WIENS and D. J. HOBAN  
 University of Manitoba and Health Sciences Centre, Winnipeg, Manitoba, Canada

## ABSTRACT

**Background:** Doripenem is a new carbapenem. As part of an annual, ongoing Canadian national surveillance study assessing antimicrobial resistance in patients in hospitals, we examined the activities of doripenem in comparison to meropenem and ertapenem and other comparators.  
**Methods:** From January 2007 through December 2009, sentinel hospitals representing 8 of 10 provinces across Canada submitted pathogens from patients attending hospital clinics, emergency rooms, medical and surgical wards, and intensive care units. Each centre was asked to submit pathogens (consecutive, one per patient/infection site) from blood, respiratory, urine and wound/infectious. A total of 18,538 isolates were collected from 2007-2009, inclusive. Susceptibility testing was performed using CLSI broth microdilution methods.

**Results:** In vitro activities (MIC50/90 µg/ml) of carbapenems were:

	Doripenem	Meropenem	Ertapenem
<i>E. coli</i> (3930)	<0.12/>0.12	<0.12/>0.12	<0.06/>0.06
<i>P. aeruginosa</i> (1476)	0.5/4	0.5/8	8/>32
<i>K. pneumoniae</i> (1128)	<0.12/>0.12	<0.12/>0.12	<0.06/>0.06
<i>E. cloacae</i> (424)	<0.12/>0.12	<0.12/>0.12	<0.06/0.5
<i>P. mirabilis</i> (288)	0.12/0.25	<0.12/>0.12	<0.06/>0.06
<i>K. oxytoca</i> (272)	<0.12/>0.12	<0.12/>0.12	<0.06/>0.06
<i>S. marcescens</i> (251)	<0.12/>0.12	<0.12/>0.12	<0.06/0.06
<i>S. maltophilia</i> (243)	>32/>32	>32/>32	>32/>32
<i>E. faecalis</i> (200)	<0.12/>0.12	<0.12/>0.12	<0.08/0.25
<i>C. freundii</i> (85)	<0.12/>0.12	<0.12/>0.12	<0.06/0.12
<i>A. baumannii</i> (63)	0.25/1	0.5/2	4/16
<i>H. influenzae</i> (60)	<0.06/0.5	<0.06/0.12	<0.03/0.12
MSSA (2697)	<0.12/>0.12	0.12/0.25	0.25/0.25
HA-MRSA (629)	8/32	16/>32	16/>32
CA-MRSA (223)	1/2	2/2	2/8
<i>S. epidermidis</i> (321)	1/16	2/32	4/>32
MSSE (268)	1/8	1/8	2/32
MRSE (45)	16/32	32/32	>32/>32
<i>S. pneumoniae</i> (1391)	<0.06/0.06	<0.06/>0.06	<0.06/0.12
<i>S. pyogenes</i> (273)	<0.06/>0.06	<0.06/>0.06	<0.06/>0.06
<i>Enterococcus</i> spp. (578)	4/8	4/16	16/32
<i>E. faecalis</i> (381)	4/8	4/8	8/16
<i>E. faecium</i> (150)	>32/>32	>32/>32	>32/>32
VR4 (34)	>32/>32	>32/>32	>32/>32

MSSA-methicillin-susceptible *Staphylococcus aureus*; HA-health-care-associated; CA-community-associated; MSSE-methicillin-susceptible *Staphylococcus epidermidis*; VRSE-vancomycin-resistant *enterococci*.

**Conclusions:** Doripenem displayed similar activity to meropenem, but was more active versus *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Carbapenem resistance in *Enterobacteriaceae* isolated from patients in Canadian hospitals is rare.

## INTRODUCTION

Polymicrobial infections and emerging antimicrobial resistance among many gram-positive and gram-negative pathogens causing intra-abdominal and complicated urinary tract infections and nosocomial/ventilator acquired pneumonia, support the development and strategic use of broad-spectrum agents such as the carbapenems. Doripenem is a new carbapenem which demonstrates the favourable characteristics of other carbapenems including broad-spectrum activity and  $\beta$ -lactamase stability (1,2). It demonstrates in vitro activity against gram-positive and gram-negative pathogens including anaerobic bacteria (1). Doripenem has potency against gram-positive cocci which is most similar to that of imipenem (greater than that of meropenem), and activity against gram-negative bacteria which is most like that of meropenem (greater than that of imipenem) (1).

The purpose of this study was to compare the activity of doripenem to comparators, against Gram-positive and Gram-negative pathogens in Canadian hospitals.

## MATERIALS & METHODS

**Bacterial Isolates:** Tertiary-care medical centres (12 in 2007, 10 in 2008, 15 in 2009) representing 8 of 10 provinces across Canada submitted pathogens from patients attending hospital clinics, emergency rooms, medical and surgical wards, and intensive care units. The sites were geographically distributed in a population-based fashion. From January 2007 through December 2009, inclusive, each study site was asked to submit clinical isolates (consecutive, one per patient, per infection site) from inpatients and outpatients with respiratory, urine, wound, and bloodstream infections. The medical centre submitted "clinically significant" isolates from patients with a presumed infectious disease. Surveillance swabs, eye, ear, nose and throat swabs were excluded. We also excluded anaerobic organisms. Isolate identification was performed by the submitting site and confirmed at the reference site as required, based on morphological characteristics and antimicrobial susceptibility patterns. Isolates were shipped on Amies semi-solid transport media to the coordinating laboratory (Health Sciences Centre, Winnipeg, Canada), subcultured onto appropriate media, and stocked in skim milk at -80°C until minimum inhibitory concentration (MIC) testing was carried out. In 2007, 2008, and 2009, 7881, 5282, and 5375 isolates were collected, respectively.

**Antimicrobial Susceptibilities:** Following 2 subcultures from frozen stock, the in vitro activity of doripenem and selected antimicrobials was determined by broth microdilution in accordance with the Clinical and Laboratory Standards Institute (CLSI) guidelines (2006 M7-A7 and M100-S16). Antimicrobial minimum inhibitory concentration (MIC) interpretive standards were defined according to CLSI breakpoints (CLSI, 2010). Susceptibility testing could not be performed with all agents due to lack of space on the susceptibility panels. Antimicrobial agents were obtained as laboratory grade powders from their respective manufacturers. Stock solutions were prepared and dilutions made as described by CLSI (M7-A7, 2006). The MICs of the antimicrobial agents for the isolates were determined using 96-well custom designed microtitre plates. These plates contained doubling antimicrobial dilutions in 100 $\mu$ l/well of culture adjusted Mueller-Hinton broth and inoculated to achieve a final concentration of approximately  $5 \times 10^5$  CFU/ml then incubated in ambient air for 24 hours prior to reading. Colony counts were performed periodically to confirm inocula. Quality control was performed using ATCC QC organisms; *S. pneumoniae* 49619, *S. aureus* 29213, *E. faecalis* 29212, *E. coli* 25922, and *P. aeruginosa* 27853.

Table 1. Doripenem in vitro activity against aerobic Gram-positive bacteria isolated from patients in Canadian hospitals in 2007-2009.

Organism (phenotype (n))	Antimicrobial Agent	MIC Range	µg/ml	MIC <sub>50</sub>	MIC <sub>90</sub>	% Susceptible
<i>S. pneumoniae</i> (1376)	Carbapenem	0.25-16	0.25	0.5	94.3	NA
	Cefazolin	0.05-16	0.03	0.03	94.3	NA
	Carbapenem	0.25-16	0.25	0.5	94.3	NA
	Carbapenem	0.04-0.08	0.02	0.02	99.4	NA
	Doripenem	0.05-0.08	0.04	0.04	99.9	NA
	Meropenem	0.04-0.08	0.04	0.04	99.9	NA
<i>S. pyogenes</i> (273)	Carbapenem	0.25	0.25	0.25	NA	NA
	Carbapenem	0.06-0.12	0.06	0.06	100	NA
	Carbapenem	0.06	0.06	0.06	100	NA
	Doripenem	0.06-0.12	0.06	0.06	100	NA
	Meropenem	0.06-0.12	0.06	0.06	100	NA
	Meropenem	0.06-0.12	0.06	0.06	100	NA
<i>E. faecalis</i> (381)	Carbapenem	0.5-128	32	64	NA	NA
	Carbapenem	0.1-128	128	128	NA	NA
	Carbapenem	0.5-32	0.5	1	NA	NA
	Carbapenem	0.5-128	0.56	0.56	NA	NA
	Doripenem	0.5-32	4	8	NA	NA
	Meropenem	0.25-32	8	16	NA	NA
<i>E. faecium</i> (150)	Carbapenem	2-128	>128	>128	NA	NA
	Carbapenem	0.25-128	128	128	NA	NA
	Carbapenem	0.5-256	>256	>256	NA	NA
	Doripenem	2-32	>32	>32	NA	NA
	Meropenem	4-32	>32	>32	NA	NA
	Meropenem	2-32	>32	>32	NA	NA

\*Carbapenem MICs interpreted using Health Canada approved breakpoints.

NA = not available.

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## CONCLUSIONS

- Doripenem displayed slightly greater activity than meropenem against Gram-positive cocci.
- Doripenem displayed very similar activity to meropenem against Enterobacteriaceae.
- Doripenem was more active versus *Pseudomonas aeruginosa* and *Acinetobacter baumannii* than meropenem.
- Carbapenem resistance (meropenem, doripenem and ertapenem) in Enterobacteriaceae isolated from patients in Canadian hospitals is rare.

## RESULTS

Table 2. Doripenem in vitro activity against aerobic Gram-negative bacteria isolated from patients in Canadian hospitals in 2007-2009.

Organism (phenotype (n))	Antimicrobial Agent	MIC Range	µg/ml	MIC <sub>50</sub>	MIC <sub>90</sub>	% Susceptible
<i>E. coli</i> (3930)	Carbapenem	0.25-16	2	8	94.3	NA
	Carbapenem	0.5-128	4	32	12.8	NA
	Carbapenem	0.25-16	0.25	0.25	99.9	NA
	Carbapenem	0.06-128	4	8	91.8	NA
	Carbapenem	0.5-128	0.06	0.06	99.97	NA
	Carbapenem	0.25-16	0.25	0.25	91.1	NA
<i>P. aeruginosa</i> (1476)	Carbapenem	0.06-0.12	0.06	0.06	100	NA
	Carbapenem	0.06-0.12	0.06	0.06	100	NA
	Carbapenem	0.06-0.12	0.06	0.06	100	NA
	Carbapenem	0.06-0.12	0.06	0.06	100	NA
	Carbapenem	0.06-0.12	0.06	0.06	100	NA
	Carbapenem	0.06-0.12	0.06	0.06	100	NA
<i>K. pneumoniae</i> (1128)	Carbapenem	0.5-32	2	8	96.2	NA
	Carbapenem	0.5-32	2	8	96.8	NA
	Carbapenem	0.25-128	0.25	0.25	98	NA
	Carbapenem	0.5-128	2	8	92.7	NA
	Carbapenem	0.06-32	0.06	0.06	96.1	NA
	Carbapenem	0.25-32	0.25	0.25	95.5	NA
<i>S. maltophilia</i> (243)	Carbapenem	0.06-0.12	0.06	0.06	99.8	NA
	Carbapenem	0.06-0.12	0.06	0.06	100	NA
	Carbapenem	0.06-0.12	0.06	0.06	100	NA
	Carbapenem	0.06-0.12	0.06	0.06	100	NA
	Carbapenem	0.06-0.12	0.06	0.06	100	NA
	Carbapenem	0.06-0.12	0.06	0.06	100	NA
<i>A. baumannii</i> (63)	Carbapenem	0.5-32	16	32	NA	NA
	Carbapenem	0.25-128	4	32	80.7	NA
	Carbapenem	0.12-32	1	2	NA	NA
	Carbapenem	0.5-128	128	128	NA	NA
	Carbapenem	0.06-32	0.25	1	53.7	NA
	Carbapenem	0.25-32	0.25	0.25	64	NA
<i>H. influenzae</i> (88)	Carbapenem	0.06-0.5	0.5	2	95.2	NA
	Carbapenem	0.06-0.5	0.5	2	95.2	NA
	Carbapenem	0.06-0.5	0.5	2	99.9	NA
	Carbapenem	0.06-0.5	0.25	0.25	100	NA
	Carbapenem	0.06-0.5	0.06	0.12	99.9	NA
	Carbapenem	0.06-0.5	0.06	0.12	99.9	NA
<i>E. aerogenes</i> (90)	Carbapenem	2-32	32	>32	7.1	NA
	Carbapenem	1-128	64	>128	0	NA
	Carbapenem	0.25-16	0.25	0.25	98.9	NA
	Carbapenem	2-32	>32	>32	7.1	NA
	Carbapenem	0.06-8	0.06	0.06	99.9	NA
	Carbapenem	0.06-8	0.06	0.06	100	NA
<i>P. aeruginosa</i> (90)	Carbapenem	0.06-0.12	0.06	0.06	100	NA
	Carbapenem	0.06-0.12	0.06	0.06	100	NA
	Carbapenem	0.06-0.12	0.06	0.06	100	NA
	Carbapenem	0.06-0.12	0.06	0.06	100	NA
	Carbapenem	0.06-0.12	0.06	0.06	100	NA
	Carbapenem	0.06-0.12	0.06	0.06	100	NA

\*Carbapenem MICs interpreted using Health Canada approved breakpoints.

NA = not available.

## REFERENCES

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