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Worldwide Summary of Doripenem Spectrum and Activity: Potencies Against 128,444 Gram-positive Pathogens

DJ FARRELL, GJ MOET, HS SADER, RN JONES

JMI Laboratories, North Liberty, Iowa, USA

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JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
319.665.3370, fax 319.665.3371
david-farrell@jmilabs.com

Abstract

Background: Doripenem (DOR) is a carbapenem approved in many countries for the treatment of hospital-acquired bacterial pneumonia (HABP), ventilator-associated pneumonia (VAP), complicated intra-abdominal infections (cIAI), and complicated urinary tract infections (cUTI). We report the in vitro antimicrobial activity of DOR tested against prevalent Gram-positive pathogens isolated worldwide.

Methods: During 2003-2009, a total of 128,444 consecutive, non-duplicate isolates from a variety of infections were collected from the following regions (n countries; n isolates): Asia Pacific (13; 20,447), Europe (15; 38,253), Latin America (5; 14,514), and North America (2; 55,230). Susceptibility (S) testing was performed using CLSI methods (M07-A8).

Results: DOR had high activity against methicillin-susceptible (MS) *S. aureus* (SA), MS-coagulase-negative staphylococci (CoNS), β-haemolytic streptococci, viridans streptococci, and *S. pneumoniae* with MIC_{90} values of ≤0.06, ≤0.06, ≤0.06, 0.25, and 0.5 µg/ml, respectively. DOR was active against a few MRSA and MR-CoNS both with an MIC_{50} of 2 µg/ml. DOR was not active against the vast majority of *E. faecium*, and had marginal activity against *E. faecalis* ($MIC_{50/90}$, 4/8 µg/ml).

Conclusions: Against this very large global population of geographically and temporally (including contemporary [2009]) diverse collection of isolates, DOR exhibited excellent potency against most Gram-positive pathogens except for MRSA, MR-CoNS and *E. faecium*. This data supports the use of DOR as empiric therapy for hospitalized patients, in whom carbapenem therapy would be warranted to treat serious and typically difficult-to-treat infections, such as HABP, VAP, cIAI, and cUTI.

Introduction

Empiric antimicrobial therapy in healthcare settings that deal with a high proportion of seriously ill patients is becoming progressively more compromised by dramatic increases in the prevalence of extended spectrum β-lactamase (ESBL)-producing Enterobacteriaceae (primarily *Escherichia coli* and *Klebsiella* spp.), constitutively-expressed chromosomal AmpC (Bush group 1 enzymes in *Enterobacter* spp., *Citrobacter* spp. and *Serratia* spp.), serine carbapenemases (primarily KPC in *Klebsiella* spp.), and multidrug-resistant (MDR) nonfermentative Gram-negative bacilli. Resistances to "third"- and "fourth-generation" cephalosporins, β-lactam/β-lactamase inhibitor combinations, fluoroquinolones and aminoglycosides have also become commonplace in various geographic regions, requiring the utilization of carbapenems, glycylcyclines, combination therapies or 'agents of last resort', such as the polymyxins.

As an antimicrobial class, carbapenems are innately stable to most β-lactamases of Ambler class A, C and D, and are widely used for serious infections involving resistant Enterobacteriaceae (including ESBL-producing and AmpC over-expressing isolates), anaerobes, *Pseudomonas aeruginosa* and *Acinetobacter* spp. Doripenem was recently approved in Europe and United States (USA) for treatment of complicated intraabdominal infections (cIAI), complicated urinary tract infections (cUTI) and in Europe and other countries, including Israel and Turkey, hospital-acquired bacterial pneumonia (HABP) – including ventilator-associated pneumonia (VAP). The agent has a spectrum and potency versus Gram-positive cocci most similar to that of imipenem, and Gram-negative activity like that of meropenem (e.g. two- to four-fold greater than imipenem). The agent is highly β-lactamase stable, is resistant to inactivation by renal dehydropeptidases and, when compared with several other anti-pseudomonal agents, including other carbapenems, has the lowest rate of spontaneously occurring resistance.

In this study, we report *in vitro* testing results from a very large global collection of Gram-positive clinical isolates collected between 2003-2009 in the SENTRY Antimicrobial Surveillance Program. Doripenem activity was also compared with that of other β-lactam agents and members of several antimicrobial classes used in the empiric or directed therapy of cIAI, cUTI and HABP (including VAP).

Methods

Bacterial Strain Collection. During 2003-2009, a total of 128,444 consecutive, non-duplicate Gram-positive isolates from a variety of infections (including HABP, VAP, cIAI, and cUTI) were collected from 233 medical centers (35 countries) in four geographic regions (Table 1). Species identifications were performed by the submitting laboratories with confirmation performed by the central monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA).

Susceptibility Test Methods. All isolates were tested by the CLSI broth microdilution method (M07-A8, 2009) using validated commercially prepared panels (TREK Diagnositcs, Cleveland, Ohio, USA) in cation-adjusted Mueller-Hinton broth (with 5% lysed horse blood added for testing of streptococci) against a variety of antimicrobial agents representing the most common classes and examples of drugs used for empiric or directed treatment of these indicated pathogens. Interpretation of MIC results was in accordance with CLSI (2010) and EUCAST (2010) published criteria. Concurrent testing of ATCC quality control (QC) strains included: *Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, and *Streptococcus pneumoniae* ATCC 49619.

Results

- Against 62,753 *S. aureus* isolates, doripenem was very active against the oxacillin-susceptible isolates (MSSA; $MIC_{50/90}$, both ≤0.06 µg/ml) but much less active against the oxacillin-resistant population ($MIC_{50/90}$, 2/>8 µg/ml; Tables 2 and 3). Similar results were observed for coagulase-negative staphylococci (CoNS; Table 2). Overall, 42.7% of isolates were oxacillin-resistant (MR) and 37.3% were levofloxacin-resistant. ≥99.9% of isolates were susceptible to vancomycin, linezolid and daptomycin (Table 3).
- Limited doripenem activity was observed against enterococci with potency being lower against *E. faecium* than *E. faecalis* (Tables 2 and 3).
- Doripenem exhibited excellent activity against 8,100 β-haemolytic streptococci ($MIC_{50/90}$, both ≤0.06 µg/ml; Tables 2 and 3). Overall, 20.8 and 9.6% of isolates were resistant to erythromycin and clindamycin, respectively (Table 3).
- Doripenem showed very good potency against 3,362 viridans group streptococci (VGS; $MIC_{50/90}$, ≤0.06/0.25 µg/ml; Tables 2 and 3). Using the MIC_{90}, doripenem was four-fold more potent than penicillin, ceftriaxone and cefipime against VGS. Against these streptococcal species, erythromycin resistance was high (43.3%, Table 3).
- Doripenem exhibited high activity against 16,232 *S. pneumoniae* ($MIC_{50/90}$, ≤0.06/0.5 µg/ml; Tables 2 and 3). Overall, 62.8 and 89.4% of isolates were susceptible to penicillin at the CLSI oral (≤0.06 µg/ml) and parenteral (≤2 µg/ml) breakpoints, respectively. Erythromycin, tetracycline and triemthoprim/sulfamethoxazole resistances were 37.4, 29.1, and 24.8%, respectively. Susceptibility rates were high for linezolid (100.0%), vancomycin (>99.9%) and levofloxacin (98.8%; Table 3).

Table 1. Distribution of 128,444 Gram-positive isolates and medical centers by geographic region and country

Region and country	Number of medical centers	Number of isolates	Region and country	Number of medical centers	Number of isolates
Asia Western Pacific			**Europe**		
Australia	12	3986	Belgium	2	1147
Hong Kong	1	472	France	6	7606
India	14	1351	Germany	4	5987
Indonesia	5	121	Greece	2	1006
Japan	27	5118	Ireland	2	2401
Korea	4	1670	Israel	1	1459
New Zealand	3	895	Italy	3	3472
P.R. China	19	4255	Poland	1	1163
Philippines	2	280	Portugal	1	310
Singapore	1	619	Russia	1	181
South Africa	1	148	Spain	3	2510
Taiwan	3	994	Sweden	2	3390
Thailand	3	538	Switzerland	1	1970
Total	95	20447	Turkey	2	2760
Latin America			UK	3	2891
Argentina	2	2779	Total	34	38253
Brazil	4	6359	**North America**		
Chile	2	2824	Canada	6	2589
Mexico	3	2394	USA	86	52641
Venezuela	1	158	Total	92	55230
Total	12	14514			

Table 2. Percent distribution of doripenem MIC values for all organisms tested (2003-2009)

	Cumulative % inhibited at doripenem MIC (µg/ml):							
Organism (no. of strains)	≤0.06	0.12	0.25	0.5	1	2	4	8
S. aureus (62,753)	56	60	64	71	77	80	83	88
MRSA (26,787)	1	6	17	33	46	54	61	71
MSSA (35,965)	97	99.5	99.9	>99.9	>99.9	>99.9	100	-
CoNS (16,283)	25	32	39	49	61	71	79	87
MR-CoNS (12,451)	5	12	21	34	49	63	73	83
MS-CoNS (3,830)	91	99	99.3	99.7	99.8	99.9	100	-
E. faecalis (13,865)	1	1	1	1	2	29	83	96
E. faecium (7,012)	1	1	1	1	1	1	2	5
ß-haemolytic strep. (8,100)	99.5	>99.9	>99.9	100	-	-	-	-
Viridans strep. (3,362)	76	87	92	94	97	98	99.3	99.4
S. pneumoniae (16,232)	72	75	85	98	99.7	99.9	>99.9	>99.9

Table 3. Antimicrobial activity of doripenem and comparator agents when tested against Gram-positive bacterial isolates

Organism (no. tested)/Antimicrobial agent	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)	Range (µg/ml)	CLSI[a] %S / %R	EUCAST[a] %S / %R
S. aureus (62,753)					
Doripenem	≤0.06	>8	≤0.06 – >8	-[b] / -	- / -
Oxacillin	0.5	>2	≤0.25 – >2	57.3 / 42.7	57.3 / 42.7
Cefepime	4	>16	≤0.12 – >16	57.3 / 42.7	57.3 / 42.7
Ceftriaxone	4	>32	≤0.25 – >32	57.3 / 42.7	57.3 / 42.7
Daptomycin	0.25	0.5	≤0.06 – 4	99.9 / -	99.9 / 0.1
Imipenem	≤0.5	>8	≤0.5 – >8	57.3 / 42.7	57.3 / 42.7
Levofloxacin	≤0.5	>4	≤0.5 – >4	61.9 / 37.3	61.9 / 37.3
Linezolid	2	2	≤0.06 – >8	>99.9 / <0.1	>99.9 / <0.1
Tetracycline	≤2	>8	≤2 – >8	88.0 / 11.5	87.3 / 12.6
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – >2	95.4 / 4.6	95.4 / 4.6
Vancomycin	1	1	≤0.12 – 4	>99.9 / 0.0	>99.9 / <0.1
Oxacillin-susceptible (35,965)					
Doripenem	≤0.06	≤0.06	≤0.06 – 4	- / -	- / -
Cefepime	2	4	≤0.12 – >16	>99.9 / < 0.1	100.0 / 0.0
Ceftriaxone	4	4	≤0.25 – 32	99.7 / 0.0	100.0 / 0.0
Daptomycin	0.25	0.5	≤0.06 – 4	>99.9 / -	>99.9 / <0.1
Imipenem	≤0.5	≤0.5	≤0.5 – 4	100.0 / 0.0	100.0 / 0.0
Levofloxacin	≤0.5	≤0.5	≤0.5 – >4	92.8 / 6.8	92.8 / 6.8
Linezolid	2	2	≤0.06 – 4	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤2	≤2	≤2 – >8	93.7 / 5.8	93.2 / 6.8
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – >2	98.5 / 1.5	98.5 / 1.5
Vancomycin	1	1	≤0.12 – 4	>99.9 / 0.0	>99.9 / <0.1
Oxacillin-resistant (26,787)					
Doripenem	2	>8	≤0.06 – >8	- / -	- / -
Daptomycin	0.25	0.5	≤0.06 – 4	99.9 / -	99.9 / 0.1
Levofloxacin	>4	>4	≤0.5 – >4	20.4 / 78.4	20.4 / 78.4
Linezolid	1	2	0.12 – >8	99.9 / 0.1	99.9 / 0.1
Tetracycline	≤2	>8	≤2 – >8	80.3 / 19.3	79.3 / 20.5
Trimethoprim/sulfamethoxazole	≤0.5	1	≤0.5 – >2	91.1 / 8.9	91.1 / 8.9
Vancomycin	1	1	≤0.12 – 4	>99.9 / 0.0	>99.9 / <0.1
Coagulase-negative staphylococci (16,283)					
Doripenem	1	>8	≤0.06 – >8	- / -	- / -
Oxacillin	>2	>2	≤0.25 – >2	23.5 / 76.5	23.5 / 76.5
Cefepime	4	>16	≤0.12 – >16	23.5 / 76.5	23.5 / 76.5
Ceftriaxone	16	>32	≤0.25 – >32	23.5 / 76.5	23.5 / 76.5
Daptomycin	0.25	0.5	≤0.06 – 4	99.8 / -	99.8 / 0.2
Imipenem	≤0.5	>8	≤0.5 – >8	23.5 / 76.5	23.5 / 76.5
Levofloxacin	4	>4	≤0.5 – >4	44.4 / 51.3	44.4 / 51.3
Linezolid	1	1	≤0.06 – >8	99.5 / 0.5	99.5 / 0.5
Tetracycline	≤2	>8	≤2 – >8	84.7 / 14.5	80.5 / 17.7
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5 – >2	61.0 / 39.0	61.0 / 39.0
Vancomycin	1	2	≤0.12 – 8	>99.9 / 0.0	99.4 / 0.6
Enterococcus faecalis (13,865)					
Doripenem	4	8	≤0.06 – >8	- / -	- / -
Ampicillin	≤1	2	≤1 – >16	99.6 / 0.4	98.6 / 0.4
Daptomycin	1	2	≤0.06 – 8	>99.9 / -	- / -
Levofloxacin	1	>4	≤0.5 – >4	65.5 / 33.9	- / -
Linezolid	1	2	≤0.06 – >8	99.8 / 0.1	99.9 / 0.1
Quinupristin/dalfopristin	>2	>2	≤0.25 – >2	0.8 / 95.4	0.8 / 95.4
Teicoplanin	≤2	≤2	≤2 – >16	97.6 / 2.3	97.4 / 2.6
Vancomycin	1	2	≤0.12 – >16	96.6 / 3.1	96.6 / 3.4
Enterococcus faecium (7,012)					
Doripenem	>8	>8	≤0.06 – >8	- / -	- / -
Ampicillin	>16	>16	≤1 – >16	8.1 / 91.9	7.3 / 91.9
Daptomycin	2	4	≤0.06 – >8	99.7 / -	- / -
Levofloxacin	>4	>4	≤0.5 – >4	9.9 / 86.2	- / -
Linezolid	1	2	0.25 – >8	98.7 / 0.9	99.1 / 0.9
Quinupristin/dalfopristin	1	2	≤0.25 – >2	80.4 / 10.0	80.4 / 10.0
Teicoplanin	≤2	>16	≤2 – >16	57.3 / 39.0	56.3 / 43.7
Vancomycin	1	>16	≤0.12 – >16	53.4 / 45.6	53.4 / 46.6
β-haemolytic streptococci (8,100)[c]					
Doripenem	≤0.06	≤0.06	≤0.06 – 0.5	- / -	100.0 / 0.0
Penicillin	≤0.015	0.06	≤0.015 – 1	99.9 / -	>99.9 / <0.1
Cefepime	≤0.12	≤0.12	≤0.12 – 2	99.9 / -	>99.9 / <0.1
Ceftriaxone	≤0.25	≤0.25	≤0.25 – 4	99.9 / -	>99.9 / <0.1
Clindamycin	≤0.25	0.5	≤0.25 – >2	89.9 / 9.6	90.4 / 9.6
Daptomycin	≤0.06	0.25	≤0.06 – 1	100.0 / -	100.0 / 0.0
Erythromycin	≤0.25	>2	≤0.25 – >2	78.6 / 20.8	78.6 / 20.8
Levofloxacin	≤0.5	1	≤0.5 – >4	98.5 / 1.4	95.3 / 1.5
Linezolid	1	1	≤0.06 – 2	100.0 / -	100.0 / 0.0
Vancomycin	0.5	0.5	≤0.12 – 1	100.0 / -	100.0 / 0.0
Viridans streptococci (3,362)[d]					
Doripenem	≤0.06	0.25	≤0.06 – >8	- / -	96.8 / 3.2
Penicillin	0.06	1	≤0.03 – >32	73.9 / 5.4	81.5 / 5.4
Cefepime	≤0.12	1	≤0.12 – >16	92.1 / 3.6	86.6 / 13.4
Ceftriaxone	≤0.25	1	≤0.25 – >32	92.4 / 4.1	88.0 / 12.0
Clindamycin	≤0.25	>2	≤0.25 – >2	88.2 / 11.1	88.9 / 11.1
Daptomycin	0.25	0.5	≤0.06 – 2	99.6 / -	- / -
Erythromycin	≤0.25	>2	≤0.25 – >2	54.7 / 43.3	- / -
Levofloxacin	1	2	≤0.5 – >4	94.3 / 4.6	- / -
Linezolid	1	1	≤0.06 – 8	>99.9 / -	- / -
Vancomycin	0.5	1	≤0.12 – 2	99.9 / -	100.0 / 0.0
S. pneumoniae (16,232)					
Doripenem	≤0.06	0.5	≤0.06 – 4	- / -	99.6 / 0.4
Penicillin[e]	≤0.03	4	≤0.03 – >4	89.4 / 1.1	- / -
Penicillin[f]	≤0.03	4	≤0.03 – >4	62.8 / 21.0	62.8 / 10.6
Cefepime	≤0.12	1	≤0.12 – >16	91.5 / 1.0	91.5 / 1.0
Ceftriaxone	≤0.25	1	≤0.25 – >32	91.9 / 2.0	79.0 / 2.0
Clindamycin	≤0.25	>1	≤0.25 – >1	76.8 / 22.8	77.2 / 22.8
Erythromycin	≤0.25	>2	≤0.25 – >2	62.2 / 37.4	62.2 / 37.4
Levofloxacin	1	1	≤0.5 – >4	98.8 / 1.0	98.8 / 1.2
Linezolid	1	1	≤0.12 – 2	100.0 / -	100.0 / 0.0
Tetracycline	≤2	>8	≤2 – >8	70.1 / 29.1	70.0 / 29.9
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5 – >2	64.8 / 24.8	71.9 / 24.8
Vancomycin	≤1	≤1	≤1 – >1	>99.9 / -	100.0 / 0.0

a. Criteria as published by the CLSI [2010] and EUCAST [2009], for staphylococci only β-lactam susceptibility should be directed by the oxacillin test results.
b. - = No breakpoint has been established.
c. Includes: *Streptococcus dysgalactiae* (200 isolates), *S. equi* (four isolates), *S. equisimilis* (20 isolates), Group A *Streptococcus* (3222 isolates), Group B *Streptococcus* (3519 isolates), Group C *Streptococcus* (285 isolates), Group F *Streptococcus* (55 isolates), Group G *Streptococcus* (757 isolates), and unspeciated beta-haemolytic streptococci (38 isolates).
d. Includes: *Streptococcus acidominimus* (five isolates), *S. anginosus* (305 isolates), *S. bovis* (225 isolates), *Streptococcus canis* (1 isolate), *Streptococcus constellatus* (153 isolates), *S. equinus* (10 isolates), *S. gallolyticus* (37 isolates), *S. gordonii* (17 isolates), *S. intermedius* (66 isolates), *S. milleri* (104 isolates), *S. mitis* (539 isolates), *S. mutans* (20 isolates), *S. oralis* (209 isolates), *S. parasanguinis* (81 isolates), *S. pasteurianus* (12 isolates), *S. porcinus* (three isolates), *S. salivarius* (168 isolates), *S. sanguinis* (154 isolates), *S. sobrinus* (one isolate), *S. thermophilus* (two isolates), *S. uberis* (eight isolates), *S. vestibularis* (24 isolates), unspeciated streptococci (40 isolates), unspeciated alpha-haemolytic streptococci (54 isolates), and unspeciated viridans group streptococci (1124 isolates).
e. Criteria as published by the CLSI [2010] for 'Penicillin parenteral (non-meningitis)'.
f. Criteria as published by the CLSI [2010] for 'Penicillin (oral penicillin V)'.

Conclusions

- Against a very large, geographically diverse collection of contemporary Gram-positive clinical isolates, doripenem exhibited excellent activity against oxacillin-susceptible staphylococci and β-haemolytic streptococci, but activity was compromised against oxacillin-resistant staphylococci and most enterococci. Doripenem demonstrated very good potency against *S. pneumoniae* (MIC_{90}, 0.5 µg/ml).
- This data define doripenem activity against the vast majority of Gram-positive organisms on a global scale, and is potentially useful in empiric therapy decisions to treat hospitalized patients with serious and typically difficult-to-treat (MDR) infections, such as HABP, VAP, cIAI, and cUTI.

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