1179

Antimicrobial Activity and Spectrum of Doripenem against Contemporary (2010) Clinical Bacterial Pathogens from Europe

DJ FARRELL, GJ MOET, HS SADER, RN JONES
JMI Laboratories, North Liberty, IA

ECCMID 2011
JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
319.665.3370, fax 319.665.3371
david-farrell@jmilabs.com

Abstract

Objectives: To evaluate the in vitro antimicrobial activity of doripenem (DOR) tested against prevalent Gram-negative and -positive pathogens isolated across Europe (EU) during 2010. DOR is an approved carbapenem in EU for the treatment of nosocomial pneumonia (NP), including ventilator-associated pneumonia (VAP), complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI).

Methods: A total of 10,947 consecutive, non-duplicate isolates from a wide variety of infections were collected from 29 medical centers located in Europe, Turkey and Israel during 2010. Species identification was confirmed by the central monitoring laboratory and all isolates were susceptibility (S) tested using reference CLSI broth microdilution methods (M07-A8, 2009) against DOR and numerous comparison agents.

Results: Doripenem was very active against Enterobacteriaceae, inhibiting 98.9% of isolates at ≤0.5 mg/L (MIC_{90}, 0.12 mg/L). Cumulative percentage inhibition by DOR MIC for the major organism groups is shown in the Table. DOR exhibited good activity against *P. aeruginosa* ($MIC_{50/90}$, 0.5/8 mg/L) and some *Acinetobacter* spp., inhibiting 48% of isolates at ≤8 mg/L. Against Gram-positive pathogens, DOR had very high activity against methicillin-susceptible *S. aureus* (MSSA), MS-coagulase-negative staphylococci (CoNS), beta-haemolytic streptococci, and *S. pneumoniae* with MIC_{90} values of ≤0.06, ≤0.06, ≤0.06, and 0.5 mg/L, respectively. DOR was less active against MRSA and MR-CoNS with both having a MIC_{50} of 2 mg/L, as well as *E. faecalis* (MIC_{50}, 2 mg/L). DOR was not active against the vast majority of *E. faecium* (MIC_{50}, >8 mg/L, range 2->8 mg/L).

Conclusions: DOR exhibited a wide-spectrum of antimicrobial activity against 10,947 contemporary EU pathogens and excellent activity against most Gram-positive pathogens except for MRSA, MR-CoNS and Enterococci. Against Gram-negative pathogens, DOR showed excellent activity against Enterobacteriaceae and against many multidrug-resistant *P. aeruginosa* and *Acinetobacter* spp. This data supports the use of DOR as therapy for hospitalized patients, in whom carbapenem therapy would be warranted to treat serious and typically difficult-to-treat infections, such as NP, VAP, cIAI, and cUTI in the European area.

Introduction

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 nonfermentative Gram-negative bacilli are changing the face of empiric antimicrobial therapy in healthcare settings that deal with a high proportion of seriously ill patients. 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 for treatment of complicated intra-abdominal (cIAI) and urinary tract infections (cUTI) in Europe and other countries including Israel and Turkey for hospital-acquired bacterial pneumonia (HABP). 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). Doripenem 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 2010 doripenem surveillance program performed in Europe, Turkey and Israel comparing doripenem activity 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.

Materials and Methods

Bacterial Strain Collection. From the doripenem surveillance program in Europe (2010), a total of 10,947 non-duplicate, consecutive clinical isolates were submitted from 39 medical centres in the following countries (number of sites): Belgium (1), Czech Republic (1), France (5), Germany (5), Greece (1), Ireland (2), Israel (1), Italy (2), Poland (1), Portugal (1), Russia (4), Slovenia (1), Spain (4), Sweden (2), Turkey (3), the United Kingdom (4) and Ukraine (1). Isolates originated from patients with multiple infection types and were either nosocomial or community-acquired. 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 Diagnostics, Cleveland, Ohio, USA) in cation-adjusted Mueller-Hinton broth (with 2-5% lysed horse blood added for testing of streptococci or Haemophilus Test Medium for testing of other fastidious species) 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 (2011) and EUCAST (2011) published criteria. Enterobacteriaceae with elevated MIC values (≥2 mg/L) for ceftazidime or ceftriaxone or aztreonam were considered as extended-spectrum β-lactamase (ESBL)-producing phenotypes. Concurrent testing of ATCC quality control (QC) strains included: *Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *E. coli* ATCC 25922, *E. coli* ATCC 35218, *P. aeruginosa* ATCC 27853, *Streptococcus pneumoniae* ATCC 49619 and *Haemophilus influenzae* ATCC 49247.

Results

- Overall, doripenem inhibited 99.3% of the tested Enterobacteriaceae (3,311 isolates) recovered from European medical centers in 2010 at a MIC of ≤1 mg/L (Table 1). Of the doripenem resistant strains all were *K. pneumoniae* with seven each recovered from Israel and Greece as well as three from Italy and one from Poland (data not shown).
- Doripenem, imipenem, meropenem and ertapenem were the most active agents tested against the Enterobacteriaceae, inhibiting 99.3, 99.2, 99.3 and 97.8% of isolates, respectively, at EUCAST published susceptible breakpoints. The next most active agents tested were cefepime (85.2% S) and piperacillin/tazobactam (84.1% S; Table 2).
- Doripenem was very active against ESBL-phenotype (ceftazidime or ceftriaxone or aztreonam) *E. coli* (MIC_{90}, ≤0.06 mg/L; 100% inhibited at ≤0.5 mg/L) and most ESBL-phenotype *Klebsiella* spp. (MIC_{90}, 1 mg/L; Table 3).
- Doripenem demonstrated good activity against most isolates of *P. aeruginosa* (MIC_{50}, 0.5 mg/L, 70.0% susceptible by EUCAST breakpoint) but was less active against *Acinetobacter* spp. (MIC_{50}, >8 mg/L, 37.8% susceptible by EUCAST breakpoint; Table 2).
- Against staphylococci, doripenem was very active against oxacillin-susceptible isolates (MSSA and MS-CoNS; MIC_{90}, ≤0.06 mg/L) but was less active against the oxacillin-resistant isolates (MRSA and MR-CoNS; $MIC_{50/90}$, 2/>8 mg/L; Tables 1 and 2).
- Doripenem showed limited activity against *E. faecalis* ($MIC_{50/90}$, 2/4 mg/L) and less activity against *E. faecium* ($MIC_{50/90}$, >8/>8 mg/L; Tables 1 and 2).
- Doripenem exhibited good activity against both *S. pneumoniae* and *H. influenzae* with a $MIC_{50/90}$ of ≤0.06/0.5 mg/L and ≤0.06/0.25 mg/L, respectively (Tables 1 and 2).
- Against β-haemolytic streptococci (39.6% *S. agalactiae* and 37.9% *S. pyogenes*) doripenem exhibited excellent potency ($MIC_{50/90}$, ≤0.06 mg/L) with highest MIC observed at 0.25 mg/L (Tables 1 and 2).

Table 2. Antimicrobial activity of doripenem and comparator agents when tested against bacterial isolates from European medical centers

Organism (no. tested)/ Antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI[a] %S / %R	EUCAST[b] %S / %R
Enterobacteriaceae (3,311)					
Doripenem	≤0.06	0.12	≤0.06 – >8	99.3 / 0.6	99.3 / 0.5
Imipenem	≤0.12	1	≤0.12 – >8	95.4 / 0.8	99.2 / 0.4
Meropenem	≤0.12	≤0.12	≤0.12 – >8	99.2 / 0.7	99.3 / 0.5
Ertapenem	≤0.06	≤0.06	≤0.06 – >8	96.3 / 2.2	97.8 / 1.6
Ampicillin	>8	>8	≤1 – >8	26.9 / 0.0	-[c] / 73.1
Cefepime	≤0.12	8	≤0.12 – >16	90.6 / 7.3	85.2 / 10.9
Ceftazidime	0.12	16	≤0.015 – >32	86.3 / 11.5	82.8 / 13.7
Ceftriaxone	≤0.06	>8	≤0.06 – >8	80.5 / 18.6	80.5 / 18.6
Levofloxacin	≤0.5	>4	≤0.5 – >4	78.2 / 19.2	77.1 / 21.8
Pip/tazo[c]	2	32	≤0.5 – >64	88.5 / 5.9	84.1 / 11.5
Trim/sulfa[d]	≤0.5	>4	≤0.5 – >4	69.4 / 30.6	69.4 / 30.2
Acinetobacter spp. (188)					
Doripenem	>8	>8	≤0.06 – >8	- / -	37.8 / 56.9
Imipenem	>8	>8	≤0.12 – >8	41.5 / 58.0	41.0 / 58.0
Meropenem	>8	>8	≤0.12 – >8	42.0 / 54.3	39.9 / 54.3
Ertapenem	>8	>8	0.25 – >8	- / -	- / -
Amikacin	32	>32	≤0.25 – >32	45.7 / 50.0	44.1 / 54.3
Ceftazidime	>32	>32	0.25 – >32	30.3 / 63.8	- / -
Colistin	1	2	≤0.5 – >4	97.3 / 2.7	97.3 / 2.7
Levofloxacin	>4	>4	≤0.5 – >4	33.0 / 62.8	32.4 / 67.0
Pip/tazo[c]	>64	>64	≤0.5 – >64	34.6 / 65.4	- / -
Tobramycin	2	>16	≤0.12 – >16	52.7 / 44.7	52.7 / 47.3
Pseudomonas aeruginosa (633)					
Doripenem	0.5	8	≤0.06 – >8	- / -	70.0 / 10.4
Imipenem	1	>8	≤0.12 – >8	74.9 / 14.2	74.9 / 14.2
Meropenem	0.5	>8	≤0.12 – >8	80.6 / 10.3	72.2 / 10.3
Ertapenem	8	>8	0.12 – >8	- / -	- / -
Ceftazidime	2	>32	0.25 – >32	75.7 / 20.5	75.7 / 24.3
Colistin	1	2	≤0.5 – >4	99.7 / 0.2	99.7 / 0.3
Levofloxacin	≤0.5	>4	≤0.5 – >4	70.1 / 23.2	61.9 / 29.9
Pip/tazo[c]	8	>64	≤0.5 – >64	83.6 / 16.4	72.8 / 27.2
Tobramycin	0.5	>16	≤0.12 – >16	82.5 / 16.4	82.5 / 17.5
S. aureus (2,664)					
Doripenem	≤0.06	4	≤0.06 – >8	- / -	- / -
Imipenem (n=1,665)	≤0.12	2	≤0.12 – >8	74.1 / 25.9	74.1 / 25.9
Oxacillin	0.5	>2	≤0.25 – >2	74.1 / 25.9	74.1 / 25.9
Ceftriaxone	4	>8	0.5 – >8	73.3 / 25.9	74.1 / 25.9
Daptomycin	0.25	0.5	≤0.06 – 2	>99.9 / -	>99.9 / <0.1
Levofloxacin	≤0.5	>4	≤0.5 – >4	72.4 / 26.8	72.4 / 26.8
Linezolid	1	1	≤0.12 – 2	100.0 / 0.0	100.0 / 0.0
Pip/tazo[c]	1	64	≤0.5 – >64	74.1 / 25.9	74.1 / 25.9
Tetracycline	≤0.25	0.5	≤0.25 – >8	93.5 / 5.6	93.1 / 6.6
Trim/sulfa[d]	≤0.5	≤0.5	≤0.5 – >4	99.2 / 0.8	99.2 / 0.7
Vancomycin	1	1	≤0.12 – 2	100.0 / 0.0	100.0 / 0.0
Oxacillin-susceptible (MSSA; 1,974)					
Doripenem	≤0.06	≤0.06	≤0.06 – 0.5	- / -	- / -
Imipenem (n=1,225)	≤0.12	≤0.12	≤0.12 – 0.5	100.0 / 0.0	100.0 / 0.0
Cefepime	2	2	≤0.12 – 16	99.9 / 0.0	100.0 / 0.0
Ceftriaxone	4	4	0.5 – >8	98.5 / 0.1	100.0 / 0.0
Daptomycin	0.25	0.5	≤0.06 – 1	100.0 / -	100.0 / 0.0
Levofloxacin	≤0.5	≤0.5	≤0.5 – >4	93.5 / 5.7	93.5 / 5.7
Linezolid	1	1	≤0.12 – 2	100.0 / 0.0	100.0 / 0.0
Pip/tazo[c]	1	2	≤0.5 – 8	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤0.25	0.5	≤0.25 – >8	95.3 / 4.1	94.9 / 4.9
Trim/sulfa[d]	≤0.5	≤0.5	≤0.5 – >4	99.6 / 0.4	99.6 / 0.3
Vancomycin	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Oxacillin-resistant (MRSA; 690)					
Doripenem	2	>8	≤0.06 – >8	- / -	- / -
Imipenem (n=440)	1	>8	≤0.12 – >8	0.0 / 100.0	0.0 / 100.0
Daptomycin	0.25	0.5	0.12 – 2	99.9 / -	99.9 / 0.1
Levofloxacin	>4	>4	≤0.5 – >4	12.0 / 87.2	12.0 / 87.2
Linezolid	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤0.25	8	≤0.25 – >8	88.4 / 10.0	87.7 / 11.6
Trim/sulfa[d]	≤0.5	≤0.5	≤0.5 – >4	98.1 / 1.9	98.1 / 1.9
Vancomycin	1	1	≤0.12 – 2	100.0 / 0.0	100.0 / 0.0
Coagulase-negative staphylococci (658)					
Doripenem	0.5	>8	≤0.06 – >8	- / -	- / -
Imipenem (n=389)	0.25	>8	≤0.12 – >8	25.8 / 74.2	25.8 / 74.2
Oxacillin	>2	>2	≤0.25 – >2	25.8 / 74.2	25.8 / 74.2
Cefepime	4	>16	≤0.12 – >16	25.8 / 74.2	25.8 / 74.2
Ceftriaxone	>8	>8	0.5 – >8	25.8 / 74.2	25.8 / 74.2
Daptomycin	0.25	0.5	≤0.06 – 2	99.8 / -	99.8 / 0.2
Levofloxacin	4	>4	≤0.5 – >4	44.1 / 51.1	44.1 / 51.1
Linezolid	0.5	1	≤0.12 – >8	99.7 / 0.3	99.7 / 0.3
Pip/tazo[c]	2	64	≤0.5 – >64	25.8 / 74.2	25.8 / 74.2
Tetracycline	1	>8	≤0.25 – >8	86.0 / 12.0	71.6 / 16.1
Trim/sulfa[d]	≤0.5	>4	≤0.5 – >4	62.7 / 37.3	62.7 / 22.7
Vancomycin	1	2	0.25 – 4	100.0 / 0.0	99.4 / 0.6
Enterococcus faecalis (656)					
Doripenem	2	4	≤0.06 – >8	- / -	- / -
Imipenem (n=351)	1	2	≤0.12 – 8	99.8 / -	99.8 / 0.0
Ampicillin	≤1	2	≤1 – 8	100.0 / 0.0	99.8 / 0.0
Daptomycin	1	1	≤0.06 – 2	100.0 / -	- / -
Levofloxacin	1	>4	≤0.5 – >4	65.5 / 33.5	- / -
Linezolid	1	2	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Pip/tazo[c]	4	8	1 – >64	99.8 / -	99.8 / -
Teicoplanin	≤1	≤1	≤1 – >8	98.8 / 1.2	98.8 / 1.2
Vancomycin	1	2	0.25 – >16	98.8 / 1.2	98.8 / 1.2
Enterococcus faecium (363)					
Doripenem	>8	>8	2 – >8	- / -	- / -
Imipenem (n=196)	>8	>8	1 – >8	- / -	3.6 / 95.9
Ampicillin	>8	>8	≤1 – >8	5.5 / 94.5	4.7 / 94.5
Daptomycin	2	2	≤0.06 – 4	100.0 / -	- / -
Levofloxacin	>4	>4	≤0.5 – >4	7.2 / 89.0	- / -
Linezolid	1	1	0.5 – 8	99.7 / 0.3	99.7 / 0.3
Pip/tazo[c]	>64	>64	2 – >64	4.7 / -	4.7 / -
Quinupristin/dalfopristin	≤0.5	4	≤0.5 – >4	78.5 / 11.3	78.5 / 0.8
Teicoplanin	≤1	>8	≤1 – >8	84.3 / 15.7	84.0 / 16.0
Vancomycin	1	>16	≤0.12 – >16	81.0 / 18.2	81.0 / 19.0
β-haemolytic streptococci (734)					
Doripenem	≤0.06	≤0.06	≤0.06 – 0.25	- / -	100.0 / 0.0
Imipenem (n=189)	≤0.12	≤0.12	≤0.12	- / -	100.0 / 0.0
Penicillin	≤0.03	0.06	≤0.03 – 0.12	100.0 / -	100.0 / 0.0
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	92.0 / 7.6	92.4 / 7.6
Daptomycin	≤0.06	0.25	≤0.06 – 0.5	100.0 / -	100.0 / 0.0
Erythromycin	≤0.25	4	≤0.25 – >4	81.7 / 16.6	81.7 / 16.6
Levofloxacin	≤0.5	1	≤0.5 – >4	99.6 / 0.1	95.9 / 0.4
Linezolid	1	1	0.5 – 2	100.0 / -	100.0 / 0.0
Vancomycin	0.25	0.5	≤0.12 – 1	100.0 / -	100.0 / 0.0
S. pneumoniae (779)					
Doripenem	≤0.06	0.5	≤0.06 – 1	- / -	100.0 / 0.0
Imipenem (n=713)	≤0.12	0.25	≤0.12 – 1	84.3 / 1.4	100.0 / 0.0
Penicillin[e]	≤0.03	2	≤0.03 – >4	94.7 / 0.1	- / -
Penicillin[f]	≤0.03	2	≤0.03 – >4	73.3 / 15.7	73.3 / 5.3
Cefepime	≤0.12	1	≤0.12 – 4	97.4 / 0.1	97.4 / 0.1
Ceftriaxone	≤0.06	1	≤0.06 – 4	95.4 / 0.3	82.7 / 0.3
Clindamycin	≤0.25	>1	≤0.25 – >1	82.3 / 16.9	83.1 / 16.9
Erythromycin	≤0.06	>8	≤0.06 – >8	75.1 / 24.5	75.1 / 24.5
Levofloxacin	1	1	≤0.5 – >4	99.2 / 0.8	99.2 / 0.8
Linezolid	1	1	≤0.12 – 2	100.0 / -	100.0 / 0.0
Tetracycline	0.5	>8	≤0.25 – >8	77.4 / 22.0	77.2 / 22.6
Trim/sulfa[d]	≤0.5	4	≤0.5 – >4	77.2 / 16.3	82.2 / 16.3
Vancomycin	0.25	0.5	≤0.12 – 0.5	100.0 / -	100.0 / 0.0
Haemophilus influenzae (396)					
Doripenem	≤0.06	0.25	≤0.06 – 1	- / -	100.0 / 0.0
Imipenem	0.5	1	≤0.12 – 4	100.0 / -	99.7 / 0.3
Amoxicillin/clavulanate	≤1	2	≤1 – 4	100.0 / 0.0	89.9 / 10.1
Ampicillin	≤1	>8	≤1 – >8	85.6 / 12.9	85.6 / 14.4
Azithromycin	1	2	≤0.25 – >4	98.5 / -	0.5 / 1.5
Cefepime	≤0.12	≤0.12	≤0.12 – 0.5	100.0 / -	99.5 / 0.5
Ceftriaxone	≤0.06	≤0.06	≤0.06 – 0.25	100.0 / -	99.7 / 0.3
Clarithromycin	8	16	≤0.25 – >32	86.1 / 2.3	0.5 / 1.3
Levofloxacin	≤0.5	≤0.5	≤0.5	100.0 / -	100.0 / 0.0
Tetracycline	0.5	1	≤0.25 – >8	98.7 / 1.3	98.5 / 1.3
Trim/sulfa[d]	≤0.5	>4	≤0.5 – >4	73.7 / 23.0	73.7 / 25.0

a. Criteria as published by the CLSI [2011] and EUCAST [2011], for staphylococci only β-lactam susceptibility should be directed by the oxacillin test results.
b. - = No breakpoint has been established.
c. Piperacillin/tazobactam.
d. Trimethoprim/sulfamethoxazole.
e. Criteria as published by the CLSI [2011] for 'Penicillin parenteral (non-meningitis)'.
f. Criteria as published by the CLSI [2011] for 'Penicillin (oral penicillin V)'.

Table 1. Frequency of occurrence and cumulative % distribution of doripenem MIC values for all European organisms tested (2010)

Organisms (no. tested)	No. (cumulative %) of isolates inhibited at doripenem MIC (mg/L): ≤0.06	0.12	0.25	0.5	1	2	4	8	>8
Gram-negative									
Enterobacteriaceae (3,311)	2,883 (87.1)	269 (95.2)	96 (98.1)	25 (98.9)	14 (99.3)	4 (99.4)	5 (99.5)	3 (99.6)	12 (100.0)
E. coli (1,812)	1,793 (99.0)	15 (99.8)	1 (99.8)	3 (100.0)					
Klebsiella spp. (672)	611 (90.9)	21 (94.1)	3 (94.5)	10 (96.0)	8 (97.2)	1 (97.3)	5 (98.1)	3 (98.5)	10 (100.0)
Acinetobacter spp. (188)	5 (2.7)	25 (16.0)	19 (26.1)	11 (31.9)	11 (37.8)	5 (40.4)	5 (43.1)	10 (48.4)	97 (100.0)
P. aeruginosa (633)	37 (5.9)	101 (21.8)	117 (40.3)	119 (59.1)	69 (70.0)	43 (76.8)	81 (89.6)	36 (95.3)	30 (100.0)
H. influenzae (396)	200 (50.5)	130 (83.3)	28 (90.4)	36 (99.5)	2 (100.0)				
Gram-positive									
S. aureus (2,664)	1,958 (73.5)	72 (76.2)	91 (79.6)	104 (83.5)	51 (85.4)	81 (88.5)	95 (92.0)	76 (94.9)	136 (100.0)
Oxacillin-susceptible (1,974)	1,938 (98.2)	29 (99.7)	6 (99.9)	1 (100.0)					
Oxacillin-resistant (690)	20 (2.9)	43 (9.1)	85 (21.5)	103 (36.4)	51 (43.8)	81 (55.5)	95 (69.3)	76 (80.3)	136 (100.0)
Coagulase-neg. staphylococci (658)	194 (29.5)	44 (36.2)	31 (40.9)	65 (50.8)	76 (62.3)	71 (73.1)	38 (78.9)	49 (86.3)	90 (100.0)
Oxacillin-susceptible (170)	164 (96.5)	6 (100.0)							
Oxacillin-resistant (488)	30 (6.2)	38 (13.9)	31 (20.3)	65 (33.6)	76 (49.2)	71 (63.7)	38 (71.5)	49 (81.6)	90 (100.0)
E. faecalis (656)	1 (0.2)	0 (0.2)	0 (0.2)	1 (0.3)	8 (1.5)	328 (51.5)	279 (94.1)	36 (99.5)	3 (100.0)
E. faecium (363)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)	4 (1.7)	10 (4.4)	347 (100.0)
S. pneumoniae (779)	619 (79.5)	19 (81.9)	48 (88.1)	71 (97.2)	22 (100.0)				
β-haemolytic streptococci (734)	731 (99.6)	2 (99.9)	1 (100.0)						

Table 3. Antimicrobial activity of doripenem tested against Enterobacteriaceae from Europe expressing an ESBL phenotype (ceftazidime or ceftriaxone or aztreonam ≥2 mg/L)

Organism (no. tested)	MIC (mg/L) 50%	90%	Cum. % inhibited at MIC (mg/L) ≤0.06	0.12	0.25	0.5	1	2	4	8
E. coli										
All (1812)	≤0.06	≤0.06	99.0	99.8	99.8	100				
ESBL (275)	≤0.06	≤0.06	97.8	99.6	99.6	100				
Klebsiella spp.										
All (672)	≤0.06	≤0.06	90.9	94.1	94.5	96.0	97.2	97.3	98.1	98.5
ESBL (181)	≤0.06	1	74.6	80.1	81.8	86.7	90.6	90.6	92.8	94.5

Conclusions

- Against Enterobacteriaceae collected in 2010 in European medical centers, doripenem inhibited 99.3% at the EUCAST and CLSI susceptible breakpoints (≤ 1 mg/L), and was very active against most strains expressing an ESBL-phenotype.
- Doripenem demonstrated good activity against *P. aeruginosa* and some *Acinetobacter* spp. with only 70.0% and 37.8% being classified susceptible by EUCAST breakpoints, respectively.
- Excellent doripenem activity was observed against oxacillin-susceptible staphylococci and β-haemolytic streptococci, but activity was reduced against oxacillin-resistant staphylococci. Doripenem was not active against *E. faecium*.
- Doripenem demonstrated excellent potency against the major bacterial respiratory tract infection pathogens, *S. pneumoniae* and *H. influenzae*.
- Doripenem represents a good alternative choice for broad-spectrum coverage of indicated Gram-positive and –negative pathogens prevalent in European patients with CUTI, CIAI and NP including VAP.

Acknowledgment

The study was supported by Janssen Pharmaceuticals.

Selected References

1. Chastre J, Wunderink R, Prokocimer P, Lee M, Kaniga K, Friedland I (2008) Efficacy and safety of intravenous infusion of doripenem versus imipenem in ventilator-associated pneumonia: a multicenter, randomized study. *Crit Care Med* 36(4):1089-96.
2. Clinical and Laboratory Standards Institute (2009). *M07-A8, Methods of dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard-seventh edition.* Wayne, PA: CLSI.
3. Clinical and Laboratory Standards Institute (2011). *M100-S21, Performance standards for antimicrobial susceptibility testing, 21st informational supplement.* Wayne, PA: CLSI.
4. Davies TA, Shang W, Bush K, Flamm RK (2008). Affinity of doripenem and comparators to penicillin-binding proteins in *Escherichia coli* and *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother* 52: 1510-1512.
5. EUCAST (2011). Clinical MIC breakpoints. <http://www.eucast.org/clinical_breakpoints/> January, 2011.
6. Fritsche TR, Stilwell MG, Jones RN (2005). Antimicrobial activity of doripenem (S-4661): A global surveillance report (2003). *Clin Microbiol Infect* 11: 974-984.
7. Jones RN, Sader HS, Fritsche TR (2005). Comparative activity of doripenem and three other carbapenems tested against Gram-negative bacilli with various beta-lactamase resistance mechanisms. *Diagn Microbiol Infect Dis* 52: 71-74.
8. Lucasti C, Jasovich A, Umeh O, Jiang J, Kaniga K, Friedland I (2008) Efficacy and tolerability of IV doripenem versus meropenem in adults with complicated intra-abdominal infection: a phase III, prospective, multicenter, randomized, double-blind, noninferiority study. *Clin Ther* 30(5):868-83.
9. Mushtaq S, Ge Y, Livermore DM (2004). Comparative activities of doripenem versus isolates, mutants, and transconjugants of *Enterobacteriaceae* and *Acinetobacter* spp. with characterized ß-lactamases. *Antimicrob Agents Chemother* 48: 1313-1319.
10. Réa-Neto A, Niederman M, Lobo SM, Schroeder E, Lee M, Kaniga K, Ketter N, Prokocimer P, Friedland I (2008) Efficacy and safety of doripenem versus piperacillin/tazobactam in nosocomial pneumonia: a randomized, open-label, multicenter study. *Curr Med Res Opin* 24:2113-26.