In Vitro Activities of Doripenem and Six Comparator Drugs against 423 Aerobic and Anaerobic Bacterial Isolates from Infected Diabetic Foot Wounds[▽]

Ellie J. C. Goldstein,^{1,2*} Diane M. Citron,¹ C. Vreni Merriam,¹ Yumi A. Warren,¹
Kerin L. Tyrrell,¹ and Helen T. Fernandez¹

R M Alden Research Laboratory, Santa Monica, California 90404,¹ and UCLA School of
Medicine, Los Angeles, California 90095²

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Against 182 anaerobe and 241 aerobe strains obtained from diabetic foot infections, doripenem was the most active carbapenem against *Pseudomonas aeruginosa* (MIC₉₀, 2 µg/ml), more active than imipenem against *Proteus mirabilis*, and ertapenem was more active against *Escherichia coli* and *Klebsiella* spp. The MIC₅₀ and MIC₉₀ values were ≤0.125 µg/ml for methicillin-sensitive *Staphylococcus aureus* and all streptococci and 0.25/1 for *Bacteroides fragilis*.

Diabetic foot infections (DFIs) are common complications and account for ~20% of all hospitalizations for the >20 million diabetics in the United States (3). Although early-stage DFIs are generally monobacterial due to *Staphylococcus aureus*, more advanced DFIs, especially those associated with vascular insufficiency, usually involve aerobic gram-negative rods and anaerobes (9, 10), with an average of 4.1 to 5.8 bacterial species per specimen, composed of one to eight aerobe species and one to nine anaerobe species (4, 9). The Infectious Diseases Society of America guidelines (15) recommend that moderate to severe DFIs receive parenteral therapy, including carbapenems.

Doripenem is a synthetic, 1-β-methyl parenteral carbapenem with broad activity against gram-positive and gram-negative aerobic pathogens, including some carbapenem-resistant *Enterobacteriaceae* and *Pseudomonas aeruginosa* strains, as well as anaerobic bacteria (1, 2, 8, 11–13, 18), and would seem to have therapeutic potential in mixed aerobic-anaerobic diabetic foot infections. Therefore, we tested it against 182 anaerobic and 241 aerobic strains recovered from patients with symptomatic DFIs.

The isolates (Table 1) were collected between 2001 and 2007 from various studies and were identified by standard criteria (14, 16) and by molecular techniques for unusual isolates. The carbapenem standard laboratory powders were obtained from their manufacturers; ampicillin and clindamycin were obtained from Sigma Chemicals, St. Louis, MO.

Frozen cultures of anaerobes were transferred twice on brucella agar supplemented with hemin, vitamin K₁, and 5% sheep blood to assure purity and good growth. Susceptibility testing was performed by the agar dilution method according to Clinical and Laboratory Standards Institute standard M11-A7 (7). Serial twofold dilutions of antimicrobial agents were prepared

on the day of the test and added to the molten agar to prepare the plates. Inocula were applied with a Steers replicator (Craft Machine, Inc., Chester, PA) to a final concentration of 10⁵ CFU/spot. Control plates without antimicrobial agents were inoculated before and after each set of drug-containing plates. Plates were incubated at 37°C for 44 to 48 h in an anaerobic chamber (Anaerobe Systems, Morgan Hill, CA). The MIC was defined as the lowest concentration of an agent that yielded no growth or a marked change in the appearance of growth compared to the control plates.

Aerobic isolates were subcultured onto Trypticase soy blood agar and tested by the broth microdilution method using cation-adjusted Muller-Hinton broth, with lysed horse blood supplementation for streptococci and corynebacteria (5, 6). The trays were prepared in-house with serial twofold dilutions of the drugs by using a Quick-Spense apparatus (Sandy Springs Instrument Co., Germantown, MD) and stored at –70°C until use. Colonies were suspended from overnight growth and added to the trays for a final inoculum of approximately 5 × 10⁵ CFU/ml. The trays were examined after 18 to 24 h of incubation at 37°C (up to 48 h for some *Corynebacterium* strains). Quality control strains tested included *S. aureus* ATCC 29213, *Escherichia coli* ATCC 25922, *Bacteroides fragilis* ATCC 25285, and *Clostridium difficile* ATCC 700057.

The results of our study are presented in Table 1. The determined doripenem MICs for the quality control strains were as follows: *S. aureus*, 0.03 µg/ml (three times) and ≤0.015 µg/ml (twice); *E. coli*, ≤0.015 µg/ml (twice) and 0.03 µg/ml (once); *Enterococcus faecalis*, 2 µg/ml (three times) and 4 µg/ml (once); *B. fragilis*, 0.125 µg/ml (three times); and *C. difficile*, 2 µg/ml (three times).

Doripenem was the most active carbapenem against *P. aeruginosa* (MIC₉₀, 2 µg/ml); it was fourfold more active than imipenem and twice as active as meropenem. Doripenem was more active (MIC₉₀, 0.25 µg/ml) than imipenem (MIC₉₀, 4 µg/ml) against *Proteus mirabilis* and generally equivalent to ertapenem and meropenem (MIC₉₀, 0.125 µg/ml). The doripenem MICs for all other enteric rods (*E. coli*, *Enterobacter* spp., and *Klebsiella* spp.) were ≤0.25 µg/ml. It was also active

* Corresponding author. Mailing address: R M Alden Research Laboratory, 2021 Santa Monica Blvd., 740 East, Santa Monica, CA 90404. Phone: (310) 315-1511. Fax: (310) 315-3662. E-mail: ejcgmd@aol.com.

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TABLE 1. Comparative in vitro activity [] of doripenem against 251 aerobic and 192 anaerobic strains isolated from pretreatment cultures of patients with diabetic foot infections

Organism (no. of isolates) and antimicrobial agent	MIC (μg/ml)			% Resistant ^a
	Range	MIC ₅₀	MIC ₉₀	
Aerobes				
<i>Escherichia coli</i> (15)				
Doripenem	≤0.015–0.06	0.03	0.03	0
Ertapenem	≤0.015–1	≤0.015	0.06	0
Imipenem	0.125–1	0.125	0.25	0
Meropenem	≤0.015–0.06	0.03	0.03	0
Ampicillin/sulbactam	2–>64	32	>64	60
Piperacillin-tazobactam	1–>128	2	128	33
<i>Enterobacter</i> spp. (15) ^b				
Doripenem	0.03–0.25	0.06	0.25	0
Ertapenem	≤0.015–4	0.06	0.5	7
Imipenem	0.25–2	1	2	0
Meropenem	0.03–0.5	0.06	0.5	0
Ampicillin/sulbactam	4–>64	16	64	67
Piperacillin-tazobactam	1–128	4	64	13
<i>Klebsiella</i> spp. (15) ^c				
Doripenem	0.06–0.125	0.06	0.125	0
Ertapenem	≤0.015–0.03	≤0.015	≤0.015	0
Imipenem	0.125–1	0.25	1	0
Meropenem	0.03–0.125	0.03	0.06	0
Ampicillin/sulbactam	4–32	8	16	27
Piperacillin-tazobactam	1–16	2	4	0
<i>Proteus-Providencia</i> group spp. (15) ^d				
Doripenem	0.03–0.5	0.125	0.25	0
Ertapenem	≤0.015–0.25	≤0.015	0.25	0
Imipenem	0.06–4	0.5	4	0
Meropenem	≤0.015–0.25	0.06	0.125	0
Ampicillin/sulbactam	0.5–64	8	64	27
Piperacillin-tazobactam	0.25–1	0.25	0.5	0
<i>Pseudomonas aeruginosa</i> (15)				
Doripenem	0.125–4	0.25	2	7
Ertapenem	2–>32	8	32	NA ^m
Imipenem	0.5–16	2	8	13
Meropenem	0.125–16	0.5	4	7
Ampicillin/sulbactam	64–>64	>64	>64	NA
Piperacillin-tazobactam	4–32	8	16	0
<i>Corynebacterium amycolatum</i> (14)				
Doripenem	0.06–>32	0.5	2	NA
Ertapenem	0.5–>32	2	8	NA
Imipenem	0.03–>32	0.06	2	7
Meropenem	0.06–>32	0.5	2	7
Ampicillin/sulbactam	0.125–>64	1	8	7
Piperacillin-tazobactam	≤0.06–>128	4	32	21
Clindamycin	1–>64	>64	>64	100
<i>Corynebacterium</i> species, group I (14) ^e				
Doripenem	0.25–>32	1	8	NA
Ertapenem	0.5–>32	1	32	NA
Imipenem	0.06–>32	0.25	32	30
Meropenem	0.125–>32	1	16	20
Ampicillin/sulbactam	1–>64	>64	>64	80
Piperacillin-tazobactam	8–>128	>128	>128	90
Clindamycin	>64–>64	>64	>64	100
<i>Corynebacterium</i> species, group II (18) ^f				
Doripenem	≤0.015–0.25	0.125	0.25	NA
Ertapenem	≤0.015–1	0.5	1	NA
Imipenem	≤0.015–0.125	0.03	0.125	0
Meropenem	≤0.015–0.25	0.125	0.25	0
Ampicillin-sulbactam	≤0.015–2	0.5	2	0
Piperacillin-tazobactam	≤0.06–32	4	16	17
Clindamycin	≤0.06–>64	2	>64	78

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TABLE 1—Continued

Organism (no. of isolates) and antimicrobial agent	MIC (μg/ml)			% Resistant ^a
	Range	MIC ₅₀	MIC ₉₀	
<i>Staphylococcus aureus</i> , methicillin resistant (18)				
Doripenem	0.06–16	0.5	8	100
Ertapenem	0.5–>32	2	>32	100
Imipenem	0.06–16	0.25	4	100
Meropenem	0.25–32	2	16	100
Ampicillin/sulbactam	4–16	8	16	100
Piperacillin-tazobactam	8–128	64	128	100
Clindamycin	0.125–>64	0.125	>64	39
<i>Staphylococcus aureus</i> , methicillin sensitive (41)				
Doripenem	≤0.015–0.06	0.03	0.03	0
Ertapenem	0.125–0.5	0.125	0.25	0
Imipenem	≤0.015–0.03	≤0.015	0.03	0
Meropenem	0.06–0.25	0.06	0.125	0
Ampicillin/sulbactam	0.06–8	1	4	0
Piperacillin-tazobactam	0.25–8	1	2	0
Clindamycin	0.125–0.25	0.125	0.25	0
<i>Staphylococcus epidermidis</i> (15)				
Oxacillin				67
Doripenem	≤0.015–2	0.25	2	67
Ertapenem	0.25–8	2	8	67
Imipenem	≤0.015–0.5	0.125	0.5	67
Meropenem	0.06–4	1	4	67
Ampicillin/sulbactam	≤0.03–4	4	4	67
Piperacillin-tazobactam	≤0.06–4	1	4	67
Clindamycin	0.125–>64	0.25	>64	33
<i>Staphylococcus haemolyticus</i> (15)				
Oxacillin				73
Doripenem	0.125–32	0.5	16	73
Ertapenem	0.5–>32	4	>32	73
Imipenem	≤0.015–>32	0.06	16	73
Meropenem	0.06–>32	1	32	73
Ampicillin/sulbactam	1–16	4	16	73
Piperacillin-tazobactam	1–128	8	128	73
Clindamycin	≤0.06–>64	0.125	8	13
<i>Staphylococcus lugdunensis</i> (15)				
Oxacillin				0
Doripenem	0.03–0.25	0.125	0.125	0
Ertapenem	0.5–2	0.5	1	0
Imipenem	≤0.015–0.125	0.03	0.06	0
Meropenem	0.125–0.5	0.25	0.5	0
Ampicillin/sulbactam	0.06–8	0.5	4	0
Piperacillin-tazobactam	0.2–4	2	4	0
Clindamycin	≤0.06–>64	0.125	>64	13
<i>Streptococcus agalactiae</i> (15)				
Doripenem	≤0.015–0.03	≤0.015	0.03	0
Ertapenem	0.06–0.06	0.06	0.06	0
Imipenem	≤0.015–0.03	≤0.015	≤0.015	0
Meropenem	0.03–0.06	0.06	0.06	0
Ampicillin/sulbactam	0.06–0.125	0.125	0.125	0
Piperacillin-tazobactam	0.25–0.5	0.25	0.5	0
Clindamycin	≤0.06–>64	0.125	>64	33
<i>Streptococcus</i> spp. (15) ^g				
Doripenem	≤0.015	≤0.015	≤0.015	0
Ertapenem	≤0.015	≤0.015	≤0.015	0
Imipenem	≤0.015	≤0.015	≤0.015	0
Meropenem	≤0.015	≤0.015	≤0.015	0
Ampicillin/sulbactam	≤0.03	≤0.03	≤0.03	0
Piperacillin-tazobactam	≤0.06	≤0.06	≤0.06	0
Clindamycin	≤0.06–>64	0.125	>64	13

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TABLE 1—Continued

Organism (no. of isolates) and antimicrobial agent	MIC (μg/ml)			% Resistant ^a
	Range	MIC ₅₀	MIC ₉₀	
Anaerobes				
<i>Bacteroides fragilis</i> (10)				
Doripenem	0.25–0.25	0.25	0.25	0
Ertapenem	0.25–1	0.25	1	0
Imipenem	0.03–0.125	0.125	0.125	0
Meropenem	0.125–0.25	0.125	0.25	0
Ampicillin/sulbactam	1–16	1	4	0
Piperacillin-tazobactam	0.125–2	0.25	0.25	0
Clindamycin	0.125–>64	0.5	2	10
Metronidazole	0.5–1	0.5	1	0
<i>Bacteroides fragilis</i> group (15) ^h				
Doripenem	0.25–1	0.25	1	0
Ertapenem	0.25–4	1	2	0
Imipenem	0.03–1	0.5	1	0
Meropenem	0.06–1	0.25	1	0
Ampicillin/sulbactam	0.5–16	4	16	0
Piperacillin-tazobactam	0.25–16	2	16	0
Clindamycin	≤0.03–>64	2	>64	20
Metronidazole	0.125–1	0.5	1	0
<i>Porphyromonas</i> spp. (17) ⁱ				
Doripenem	≤0.015–0.06	≤0.015	0.03	0
Ertapenem	≤0.015–0.125	≤0.015	0.06	0
Imipenem	≤0.015–0.03	<0.015	≤0.015	0
Meropenem	≤0.015–0.125	≤0.015	≤0.015	0
Ampicillin/sulbactam	≤0.03–0.25	≤0.03	0.25	0
Piperacillin-tazobactam	≤0.06	≤0.06	≤0.06	0
Clindamycin	≤0.03–64	≤0.03	64	12
Metronidazole	≤0.06–4	0.05	0.25	0
<i>Prevotella bivia</i> (14)				
Doripenem	≤0.015–0.125	0.06	0.125	0
Ertapenem	0.03–0.5	0.25	0.5	0
Imipenem	≤0.015–0.03	0.03	0.03	0
Meropenem	≤0.015–0.125	0.06	0.125	0
Ampicillin/sulbactam	≤0.03–4	1	2	0
Piperacillin-tazobactam	<0.06	≤0.06	≤0.06	0
Clindamycin	≤0.03–>64	≤0.03	>64	21
Metronidazole	0.25–4	4	4	0
<i>Clostridium perfringens</i> (10)				
Doripenem	≤0.015–0.03	≤0.015	0.03	0
Ertapenem	0.03–0.125	0.06	0.125	0
Imipenem	0.03–0.125	0.06	0.125	0
Meropenem	≤0.015	≤0.015	≤0.015	0
Ampicillin/sulbactam	≤0.03–0.125	≤0.03	0.06	0
Piperacillin-tazobactam	≤0.06–0.125	≤0.06	0.125	0
Clindamycin	≤0.03–4	1	1	0
Metronidazole	0.5–2	1	1	0
<i>Clostridium</i> spp. (13) ^j				
Doripenem	≤0.015–1	0.06	1	0
Ertapenem	≤0.015–8	0.25	2	0
Imipenem	≤0.015–2	0.25	2	0
Meropenem	≤0.015–2	0.06	1	0
Ampicillin/sulbactam	≤0.03–0.5	0.06	0.5	0
Piperacillin-tazobactam	≤0.06–8	0.5	8	0
Clindamycin	≤0.03–32	0.5	16	23
Metronidazole	≤0.06–1	0.125	0.25	0
<i>Propionibacterium acnes</i> (14)				
Doripenem	0.03–0.25	0.06	0.125	0
Ertapenem	≤0.06–0.5	0.125	0.25	0
Imipenem	≤0.015	≤0.015	≤0.015	0
Meropenem	0.06–0.5	0.125	0.25	0
Ampicillin/sulbactam	≤0.03–0.125	0.06	0.125	0

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TABLE 1—Continued

Organism (no. of isolates) and antimicrobial agent	MIC ($\mu\text{g/ml}$)			% Resistant ^a
	Range	MIC ₅₀	MIC ₉₀	
Piperacillin-tazobactam	≤ 0.06 –0.5	0.125	0.5	0
Clindamycin	≤ 0.03 –2	≤ 0.03	2	0
Metronidazole	>32–>32	>32	>32	100
<i>Anaerococcus</i> spp. (22) ^k				
Doripenem	≤ 0.015 –0.5	≤ 0.015	0.06	0
Ertapenem	≤ 0.015 –2	0.125	0.25	0
Imipenem	≤ 0.015 –0.125	≤ 0.015	0.03	0
Meropenem	≤ 0.015 –0.25	0.03	0.125	0
Ampicillin/sulbactam	≤ 0.03 –0.5	≤ 0.03	0.125	0
Piperacillin-tazobactam	≤ 0.06 –0.25	≤ 0.06	0.25	0
Clindamycin	≤ 0.03 –>64	0.125	64	18
Metronidazole	0.125–2	0.5	1	0
<i>Finegoldia magna</i> (30)				
Doripenem	≤ 0.015 –0.25	0.06	0.125	0
Ertapenem	≤ 0.015 –1	0.06	0.125	0
Imipenem	≤ 0.015 –0.25	0.03	0.06	0
Meropenem	≤ 0.015 –0.5	0.06	0.125	0
Ampicillin/sulbactam	≤ 0.03 –0.5	0.125	0.25	0
Piperacillin-tazobactam	≤ 0.06 –0.5	≤ 0.06	0.125	0
Clindamycin	≤ 0.03 –>64	0.5	2	7
Metronidazole	0.125–1	0.5	1	0
<i>Peptoniphilus asaccharolyticus</i> (20)				
Doripenem	≤ 0.015 –0.125	≤ 0.015	0.06	0
Ertapenem	≤ 0.015 –1	≤ 0.015	0.25	0
Imipenem	≤ 0.015 –0.06	≤ 0.015	0.03	0
Meropenem	≤ 0.015 –0.125	≤ 0.015	0.125	0
Ampicillin/sulbactam	≤ 0.03 –0.5	0.06	0.25	0
Piperacillin-tazobactam	≤ 0.06 –0.5	≤ 0.06	0.125	0
Clindamycin	≤ 0.03 –>64	0.125	>64	25
Metronidazole	0.125–2	0.5	2	0
<i>Peptostreptococcus</i> spp. (17) ^l				
Doripenem	0.03–0.25	0.06	0.25	0
Ertapenem	≤ 0.015 –0.5	0.25	0.5	0
Imipenem	≤ 0.015 –0.06	0.03	0.06	0
Meropenem	0.03–0.25	0.125	0.25	0
Ampicillin/sulbactam	≤ 0.03 –0.5	0.06	0.125	0
Piperacillin-tazobactam	≤ 0.06 –0.5	≤ 0.06	0.25	0
Clindamycin	≤ 0.03 –2	0.125	0.5	0
Metronidazole	0.125–1	0.25	1	0

^a For aerobes, includes the value intermediate and resistant MICs; for anaerobes, the value includes resistant MICs only.

^b *Enterobacter aerogenes* (n = 4), *E. cloacae* (n = 11).

^c *Klebsiella oxytoca* (n = 9), *K. pneumoniae* (n = 6).

^d *Proteus mirabilis* (n = 9), *P. vulgaris* (n = 3), *P. rettgeri* (n = 3).

^e *Corynebacterium aurimucosum* (n = 2), *C. jeikeium* (n = 6), *C. minutissimum* (n = 1), *C. ureolyticum* (n = 1).

^f *C. striatum* (n = 9), *C. accolans* (n = 1), *C. simulans* (n = 4), *C. xerosis* (n = 4).

^g *Streptococcus dysgalactiae* subsp. *equisimilis* (n = 12), *S. pyogenes* (n = 3).

^h *Bacteroides caccae* (n = 1), *B. ovatus* (n = 3), *B. stercoris* (n = 1), *B. thetaiotaomicron* (n = 3), *B. uniformis* (n = 1), *B. vulgatus* (n = 3), *Parabacteroides distasonis* (n = 1), *P. merdae* (n = 2).

ⁱ *Porphyromonas asaccharolytica* (n = 7), *P. somerae* (n = 10).

^j *Clostridium aminovalericum* (n = 1), *C. cadaveris* (n = 4), *C. clostridioforme* (n = 3), *C. innocuum* (n = 1), *C. malenomenatum* (n = 1), *C. sphenoides* (n = 1), *C. subterminale* (n = 2).

^k *Anaerococcus prevotii* (n = 14), *A. tetradus* (n = 6), *A. vaginalis* (n = 2).

^l *Peptostreptococcus anaerobius* (n = 9), *P. micros* (n = 8).

^m NA, not available.

against gram-positive aerobes with the exception of 3 of 42 *Corynebacterium* strains (one each of *C. amycolatum*, *C. jeikeium*, and *C. ureolyticum*) and 3 of 15 *S. haemolyticus* strains, which had MICs of ≥ 8 $\mu\text{g/ml}$. Nine corynebacterial strains, including all six strains of *C. jeikeium*, had MICs of >64 $\mu\text{g/ml}$ for ampicillin-sulbactam and ≥ 128 $\mu\text{g/ml}$ for piperacillin-tazobactam. The doripenem MICs for methicillin-suscepti-

ble *S. aureus*, *S. lugdunensis*, and all streptococci were ≤ 0.125 $\mu\text{g/ml}$. All 182 anaerobes were susceptible to doripenem at ≤ 1 $\mu\text{g/ml}$. The doripenem MIC for *B. fragilis* was 0.25 $\mu\text{g/ml}$, and the MIC₅₀ and MIC₉₀ for the *B. fragilis* group, including the clindamycin-resistant strains, were 0.25 and 1 $\mu\text{g/ml}$, respectively. This finding was similar to the activities of imipenem and meropenem but more active than ertapenem. All anaero-

bic gram-positive cocci were susceptible to doripenem at ≤ 0.5 $\mu\text{g/ml}$, including four clindamycin-resistant strains of *Anaerococcus*.

Our study concurs with those of other investigators, who also found doripenem to be active against *P. aeruginosa* strains resistant to other carbapenems (1, 8). Sayko et al. (18) concluded that, compared to other carbapenems, doripenem has "the greatest ability to prevent the emergence of resistant mutants." Likewise, Fritsche et al. (8) tested $>6,200$ strains of *Enterobacteriaceae* and found doripenem to be "4- to 32-fold more active than imipenem against wild-type isolates." We found that doripenem was more active than imipenem against *P. mirabilis*. Doripenem's MICs for all other enteric rods (*E. coli*, *E. aerogenes*, and *Klebsiella* spp.) were ≤ 0.25 $\mu\text{g/ml}$, none of which was an extended-spectrum β -lactamase producer, whereas ertapenem was twofold more active against many strains of *E. coli* and *Klebsiella*.

Jones et al. (12) tested doripenem against 10 strains of multiple-drug-resistant *Corynebacterium* species and found that only 40% were susceptible to doripenem at ≤ 4 $\mu\text{g/ml}$ but did not specify the isolates further except to say that some were *C. jeikeium*. In our study, 5 of 6 *C. jeikeium* strains were susceptible to doripenem at ≤ 1 $\mu\text{g/ml}$, as were all *C. striatum*, *C. simulans*, *C. xerosis*, and 10 of 12 *C. amycolatum* strains.

Wexler et al. (19) studied the activity of doripenem and five comparator agents against 364 anaerobes isolated from general clinical sources and found it to have "excellent activity against a broad range of anaerobes," with a geometric MIC of 0.3 $\mu\text{g/ml}$ and an MIC₉₀ of 1 $\mu\text{g/ml}$. All 182 anaerobes that we tested had doripenem MICs of ≤ 1 $\mu\text{g/ml}$. *Propionibacterium acnes* strains were all susceptible at ≤ 0.25 $\mu\text{g/ml}$. Anaerobic gram-positive cocci (*Anaerococcus prevotii*, *Anaerococcus tetradius*, *Finegoldia magna*, *Peptostreptococcus micros*, and *Peptoniphilus asaccharolyticus*) were all susceptible at ≤ 0.5 $\mu\text{g/ml}$, and all clostridia were susceptible to doripenem at ≤ 1 $\mu\text{g/ml}$. Wexler et al. (19) noted that three stains of *B. fragilis* group species required ≥ 8 μg of doripenem/ml for inhibition and suggested that "overexpression of efflux pumps might contribute to the development of resistance." Pumbwe et al. (17) confirmed that many agents, including doripenem, could select for resistance of *B. fragilis* species by overexpression of efflux pumps. We did not encounter any resistant strains perhaps due to a difference in isolate sources or patient populations in our studies.

Our study demonstrated that doripenem has excellent activity against a wide range of aerobes and anaerobes isolated from DFIs and is a promising agent for the treatment of DFIs.

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