In Vitro Activity of TD-1792, a Multivalent Glycopeptide-Cephalosporin Antibiotic, against 377 Strains of Anaerobic Bacteria and 34 Strains of *Corynebacterium* Species

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TD-1792 is a multivalent glycopeptide-cephalosporin heterodimer antibiotic with potent activity against Gram-positive bacteria. We tested TD-1792 against 377 anaerobes and 34 strains of *Corynebacterium* species. Against nearly all Gram-positive strains, TD-1792 had an MIC₉₀ of 0.25 µg/ml and was typically 3 to 7 dilutions more active than vancomycin and daptomycin.

I ncreasing resistance of Gram-positive organisms has necessitated development of new antimicrobial agents with novel mechanisms of activity to counter such strains (8, 12, 15, 21). TD-1792 is a multivalent bactericidal antibiotic that is chemically a glycopeptide-cephalosporin heterodimer (18). While its molecular mechanism of inhibition is still under investigation, it was hypothesized that the two component moieties simultaneously target D-Ala-D-Ala-containing peptidoglycan precursors and the active site of penicillin binding proteins (PBPs), resulting in potent bactericidal activity against clinically relevant Gram-positive pathogens, including multidrug-resistant organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-intermediate *S. aureus* (VISA) (3, 16). The antibacterial activity of TD-1792 cannot be reproduced by its individual components tested alone or together as separate molecules; covalent linkage of the glycopeptide and cephalosporin components is required for the potent activity of TD-1792 (2, 9, 10, 14, 22).

Anaerobic Gram-positive organisms and corynebacteria are frequently part of polymicrobial infections (17, 20). In moderate to severe diabetic foot infections, a variety of *Corynebacterium* species were reported to be present in 116 of 454 (25.6%) cases (4) and have been regarded as important pathogens (1). Many of these organisms exhibit resistance to most categories of antimicrobial agents, and some clostridia and lactobacilli are resistant to glycopeptides (11). To determine the *in vitro* activity of TD-1792, we tested 377 anaerobic isolates and 34 *Corynebacterium* species recovered from clinical infections (1), using the reference agar dilution method.

Of the isolates used in this study, 91% were recovered from polymicrobial clinical specimens, such as intra-abdominal or skin and soft tissue specimens, during 2001 to 2006. The remaining organisms were comprised of previously isolated, less frequently encountered strains, such as *Propionibacterium granulosum*, *P. avidum*, *Lactobacillus casei*, *Actinomyces viscosus*, and anaerobic Gram-positive cocci, some with previously determined unusual patterns of resistance to clindamycin or fluoroquinolones. Isolates were identified by standard methods (13, 19) and, in some instances, by 16S gene sequencing. The strains were maintained at -70°C and transferred twice on supplemented *Brucella* agar (anaerobes) or blood agar (corynebacteria) prior to testing. Quality control strains of *Clostridium difficile* (ATCC 700057) and *Staphylococcus aureus* (ATCC 29213), as well as *Bacteroides fragilis* (ATCC 25285) and *B. thetaiotaomicron* (ATCC 29741) when test-

ing anaerobic Gram-negative organisms, were included each day of testing.

The comparator antimicrobial agents were vancomycin, daptomycin, linezolid, metronidazole, ampicillin, imipenem, and piperacillin-tazobactam. The powders were obtained from their respective manufacturers or from USP (Rockville, MD) or Sigma-Aldrich (St. Louis, MO) and were reconstituted according to CLSI guidelines (6). Daptomycin was tested in media supplemented with Ca²⁺ to 50 mg/liter.

Agar dilution was performed according to standard methods (5, 6). Serial 2-fold dilutions were added to molten supplemented *Brucella* agar (anaerobes) or Mueller-Hinton blood agar (corynebacteria) to prepare the plates. The organisms were suspended in broth to achieve turbidity equal to the 0.5 McFarland standard and applied to the drug-containing plates with a Steers replicator that delivered ~10⁵ CFU/spot for anaerobes and diluted 1:10 for ~10⁴ CFU/spot for corynebacteria. Drug-free plates were included as growth controls. The anaerobic organisms were incubated at 37°C for 44 to 48 h in an anaerobic chamber and the aerobic organisms incubated at 37°C for 24 to 48 h in ambient air and then examined for growth. The MIC was defined as the concentration of antimicrobial agent that resulted in a marked reduction of growth compared to that on the drug-free control plates.

The MIC results are shown in Table 1. TD-1792 was the most active antimicrobial agent against the majority of the Gram-positive strains evaluated in this study. The activity of TD-1792 against clostridia was particularly noteworthy. All *Clostridium innocuum* isolates were susceptible to 0.125 µg/ml of TD-1792, while the MIC₉₀ for both vancomycin and daptomycin was 16 µg/ml. Against *Clostridium perfringens*, the MIC₉₀ for TD-1792 was 0.03 µg/ml, in contrast to 2 µg/ml for daptomycin. Based on the MIC₉₀, TD-1792 was 16-fold more active (MIC₉₀, 0.25 µg/ml) than vancomycin (MIC₉₀, 4 µg/ml) against *Clostridium ramosum*, all strains of which were also resistant to daptomycin (MIC₉₀, >32

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TABLE 1 *In vitro* activities of TD-1792 and seven comparator drugs against 377 anaerobes and 34 *Corynebacterium* species strains

Organism (no.) and antimicrobial agent	MIC ($\mu\text{g/ml}$)		
	Range	50%	90%
Gram-positive organisms			
<i>Actinomyces</i> spp. (46) ^a			
TD-1792	0.002–0.25	0.03	0.06
Vancomycin	0.125–1	0.5	1
Daptomycin	≤ 0.03 –>32	2	32
Linezolid	0.125–1	0.5	1
Metronidazole	0.25–>32	>32	>32
Ampicillin	≤ 0.03 –1	0.125	0.25
Imipenem	≤ 0.03 –0.5	0.06	0.25
Piperacillin-tazobactam	≤ 0.03 –4	0.25	2
<i>Clostridium clostridioforme</i> group (21) ^b			
TD-1792	0.03–0.25	0.06	0.125
Vancomycin	0.25–1	0.5	1
Daptomycin	0.125–8	2	8
Linezolid	2–>8	4	4
Metronidazole	≤ 0.03 –0.25	0.06	0.25
Ampicillin	0.25–>8	0.5	1
Imipenem	0.125–2	1	1
Piperacillin-tazobactam	0.06–8	4	8
<i>Clostridium difficile</i> (15)			
TD-1792	1	1	1
Vancomycin	1	1	1
Daptomycin	1–2	1	2
Linezolid	2	2	2
Metronidazole	≤ 0.03 –2	0.5	2
Ampicillin	0.5–2	1	2
Imipenem	2–8	4	8
Piperacillin-tazobactam	4–8	8	8
<i>Clostridium innocuum</i> (15)			
TD-1792	0.125	0.125	0.125
Vancomycin	16	16	16
Daptomycin	4–16	8	16
Linezolid	2–4	4	4
Metronidazole	0.25–2	1	2
Ampicillin	0.06–0.25	0.125	0.125
Imipenem	0.5–4	2	2
Piperacillin-tazobactam	0.125–1	0.25	0.5
<i>Clostridium perfringens</i> (15)			
TD-1792	0.008–0.03	0.015	0.03
Vancomycin	0.5–1	1	1
Daptomycin	1–2	2	2
Linezolid	1–2	2	2
Metronidazole	0.25–2	2	2
Ampicillin	≤ 0.03 –0.125	0.06	0.125
Imipenem	≤ 0.03 –0.25	0.06	0.25
Piperacillin-tazobactam	≤ 0.03 –0.06	≤ 0.03	0.06
<i>Clostridium ramosum</i> (17)			
TD-1792	0.125–0.5	0.125	0.25
Vancomycin	4	4	4
Daptomycin	32–>32	>32	>32
Linezolid	8–>8	>8	>8
Metronidazole	0.5–4	1	2
Ampicillin	≤ 0.03 –0.25	0.06	0.125
Imipenem	0.125–0.5	0.25	0.5
Piperacillin-tazobactam	≤ 0.03 –0.25	≤ 0.03	0.06
<i>Eubacterium</i> group species (31) ^c			
TD-1792	0.002–1	0.03	0.125
Vancomycin	0.25–32	1	2
Daptomycin	0.06–32	0.5	16
Linezolid	0.25–8	1	4
Metronidazole	≤ 0.03 –4	0.25	1
Ampicillin	≤ 0.03 –1	0.06	0.25
Imipenem	≤ 0.03 –0.5	0.06	0.125
Piperacillin-tazobactam	≤ 0.03 –16	0.125	1
<i>Lactobacillus</i> spp. (24) ^d			
TD-1792	0.008–>8	1	2

TABLE 1 (Continued)

Organism (no.) and antimicrobial agent	MIC ($\mu\text{g/ml}$)		
	Range	50%	90%
Vancomycin	0.25–>32	>32	>32
Daptomycin	0.25–>32	2	4
Linezolid	1–>8	4	>8
Metronidazole	1–>32	>32	>32
Ampicillin	≤ 0.03 –8	0.5	2
Imipenem	≤ 0.03 –8	0.25	2
Piperacillin-tazobactam	≤ 0.03 –16	1	4
<i>Propionibacterium</i> spp. (34) ^e			
TD-1792	0.008–0.125	0.03	0.125
Vancomycin	0.5–2	0.5	0.5
Daptomycin	0.25–4	1	2
Linezolid	0.25–1	0.5	1
Metronidazole	>32	>32	>32
Ampicillin	≤ 0.03 –1	0.06	0.25
Imipenem	≤ 0.03 –0.06	≤ 0.03	0.06
Piperacillin-tazobactam	≤ 0.03 –4	≤ 0.03	1
Anaerobic Gram-positive cocci (48) ^f			
TD-1792	≤ 0.0005 –0.5	0.004	0.03
Vancomycin	0.06–1	0.25	0.5
Daptomycin	≤ 0.03 –1	0.125	0.5
Linezolid	0.25–2	0.5	1
Metronidazole	≤ 0.03 –2	0.25	1
Ampicillin	≤ 0.03 –>8	≤ 0.03	0.25
Imipenem	≤ 0.03 –2	≤ 0.03	0.06
Piperacillin-tazobactam	≤ 0.03 –16	≤ 0.03	0.5
Resistant anaerobic Gram-positive cocci (38) ^g			
TD-1792	0.001–0.25	0.015	0.03
Vancomycin	0.06–0.5	0.25	0.5
Daptomycin	≤ 0.03 –1	0.25	1
Linezolid	0.25–2	1	2
Metronidazole	≤ 0.03 –2	0.5	2
Ampicillin	≤ 0.03 –1	0.06	0.25
Imipenem	≤ 0.03 –0.125	≤ 0.03	0.125
Piperacillin-tazobactam	≤ 0.03 –1	≤ 0.03	0.25
<i>Corynebacterium</i> spp. (34) ^m			
TD-1792	0.002–0.25	0.03	0.125
Vancomycin	0.25–1	0.25	0.5
Daptomycin	≤ 0.03 –0.5	0.06	0.25
Linezolid	0.25–1	0.5	1
Metronidazole			
Ampicillin	≤ 0.03 –32	1	>32
Imipenem	≤ 0.03 –>32	0.06	>32
Piperacillin-tazobactam	≤ 0.03 –>128	4	>128
Gram-negative organisms			
<i>Bacteroides fragilis</i> (11)			
TD-1792	>8	>8	>8
Vancomycin	8–>32	32	>32
Daptomycin	>32	>32	>32
Linezolid	2–4	4	4
Metronidazole	0.25–1	1	1
Ampicillin	1–>32	16	>32
Imipenem	≤ 0.03 –1	0.06	1
Piperacillin-tazobactam	0.125–1	0.5	0.5
<i>Bacteroides fragilis</i> group species (12) ^h			
TD-1792	>8	>8	>8
Vancomycin	16–>32	>32	>32
Daptomycin	>32	>32	>32
Linezolid	2–8	4	8
Metronidazole	0.5–2	1	2
Ampicillin	16–>32	>32	>32
Imipenem	0.125–2	0.25	1
Piperacillin-tazobactam	0.25–32	4	32
<i>Fusobacterium</i> spp. (10) ⁱ			
TD-1792	0.06–8	0.5	4
Vancomycin	32–>32	>32	>32
Daptomycin	16–>32	>32	>32

(Continued on following page)

TABLE 1 (Continued)

Organism (no.) and antimicrobial agent	MIC ($\mu\text{g/ml}$)		
	Range	50%	90%
Linezolid	0.25–1	1	1
Metronidazole	≤ 0.03 –0.25	≤ 0.03	0.125
Ampicillin	≤ 0.03 –0.25	≤ 0.03	0.125
Imipenem	≤ 0.03 –0.125	≤ 0.03	0.125
Piperacillin-tazobactam	≤ 0.03 –0.5	≤ 0.03	0.125
<i>Porphyromonas</i> spp. (12) ^k			
TD-1792	0.015–1	0.125	1
Vancomycin	1–8	2	4
Daptomycin	>32	>32	>32
Linezolid	≤ 0.03 –1	1	1
Metronidazole	≤ 0.03 –0.5	0.25	0.5
Ampicillin	≤ 0.03 –2	≤ 0.03	0.5
Imipenem	≤ 0.03	≤ 0.03	≤ 0.03
Piperacillin-tazobactam	≤ 0.03	≤ 0.03	≤ 0.03
<i>Prevotella</i> spp. (18) ^j			
TD-1792	0.25–>8	>8	>8
Vancomycin	16–>32	>32	>32
Daptomycin	>32	>32	>32
Linezolid	0.25–2	1	2
Metronidazole	0.125–4	1	4
Ampicillin	≤ 0.03 –>32	8	>32
Imipenem	≤ 0.03 –0.06	≤ 0.03	0.06
Piperacillin-tazobactam	≤ 0.03	≤ 0.03	≤ 0.03
Unusual Gram-negative spp. (10) ⁱ			
TD-1792	1–>8	>8	>8
Vancomycin	>32	>32	>32
Daptomycin	>32	>32	>32
Linezolid	2–>32	16	>32
Metronidazole	≤ 0.03 –>32	0.5	>32
Ampicillin	0.125–>32	1	>32
Imipenem	0.06–>32	0.25	8
Piperacillin-tazobactam	≤ 0.03 –>128	8	>128

^a *Actinomyces europaeus* (1), *A. gerencseriae* (2), *A. graevenitzi* (1), *A. israelii* (3), *A. meyeri* (4), *A. naeslundii* (3), *A. neuii* subsp. *anitratus* (3), *A. neuii* subsp. *neuii* (2), *A. odontolyticus* (6), *A. radingae* (1), *A. turicensis* (11), *A. viscosus* (7), *Actinomyces* species (1), and *Actinobaculum schaalii* (1).

^b *Clostridium aldenense* (5), *C. bolteae* (4), *C. citroniae* (4), *C. clostridioforme* (4), and *C. hathewayi* (4).

^c *Atopobium parvulum* (3), *A. rimae* (1), *Collinsella aerofaciens* (5), *Eggerthella lenta* (1), *Eggerthella* sp. (2), *Eubacterium cylindroides* (1), *E. limosum* (5), *Eubacterium* species (1), *Mogibacterium timidum* (3), *Pseudoramibacter alactolyticus* (4), *Slackia exigua* (3), *Solobacterium moorei* (1), and non-spore-forming anaerobic Gram-positive rod (1).

^d *Lactobacillus acidophilus* (2), *L. cateniformis* (2), *L. crispatus* (2), *L. casei* (5), *L. fermentum* (2), *L. gasseri* (2), *L. iners* (1), *L. jensenii* (2), and *L. rhamnosus* (6).

^e *Propionibacterium acnes* (25), *P. avidum* (4), *P. granulosum* (4), and *Propionibacterium* species (1).

^f *Anaerococcus lactolyticus* (2), *A. octavius* (2), *A. prevotii* (5), *A. tetradius* (4), *A. vaginalis* (3), *Finegoldia magna* (5), *Parvimonas micra* (4), *Peptoniphilus asaccharolyticus* (6), *P. harei* (2), *P. indolicus* (2), *P. ivorii* (3), *P. lacrimalis* (2), *Peptostreptococcus anaerobius* (4), *Ruminococcus gnavus* (2), and anaerobic Gram-positive cocci (2).

^g *Anaerococcus prevotii* (9), *A. tetradius* (2), *A. vaginalis* (2), *Finegoldia magna* (12), *Parvimonas micra* (2), *Peptoniphilus asaccharolyticus* (8), *P. harei* (1), *P. ivorii* (1), and *Peptostreptococcus anaerobius* (1).

^h *Bacteroides caccae* (1), *B. nordii* (1), *B. ovatus* (4), *B. thetaiotaomicron* (3), *B. vulgatus* (1), and *Parabacteroides distasonis* (2).

ⁱ *Fusobacterium necrophorum* (2) and *F. nucleatum* (8).

^j *Prevotella bivia* (9), *P. disiens* (3), *P. intermedia/nigrescens* group (1), *P. loeschei* (4), and *P. melaninogenica* (3).

^k *Porphyromonas asaccharolytica* (4), *P. gingivalis* (2), *P. somerae* (4), *P. levii* (1), and *Porphyromonas* species (1).

^l *Bacteroides ureolyticus* (1), *Bilophila wadsworthia* (2), *Desulfovibrio fairfieldensis* (1), *D. desulfuricans* (1), *Parasutterella* species (1), *Sutterella wadsworthensis* (2), and *Veillonella* species (2).

^m *Corynebacterium amycolatum* (5), *C. aurimucosum* (3), *C. minutissimum* (2), *C. tuberculostearicum* (5), *C. accolens* (1), *C. jeikeium* (3), *C. pseudogenitalium* (2), *C. urealyticum* (1), *C. sanguinis* (4), *C. striatum* (4), *C. xerosis* (2), and *Corynebacterium* species (1).

$\mu\text{g/ml}$) and linezolid (MIC_{90} , >8 $\mu\text{g/ml}$). However, TD-1792 was less potent against *C. difficile* (MIC_{90} , 1 $\mu\text{g/ml}$), and its activity was similar to those of vancomycin (MIC_{90} , 1 $\mu\text{g/ml}$) and daptomycin (MIC_{90} , 2 $\mu\text{g/ml}$).

All five strains of *L. casei* tested were resistant to vancomycin (MIC > 32 $\mu\text{g/ml}$). Four of these had a TD-1792 MIC of 1 $\mu\text{g/ml}$, and one had a TD-1792 MIC of >8 $\mu\text{g/ml}$. The latter strain of *L. casei* was also resistant to ampicillin, imipenem, and piperacillin-tazobactam. The identity of this isolate was confirmed by 16S rRNA gene sequencing.

TD-1792 was equally effective against susceptible and resistant anaerobic Gram-positive cocci; the TD-1792 MIC_{90} was 0.03 $\mu\text{g/ml}$ for both 48 susceptible strains and 38 strains previously profiled with resistance to clindamycin, tetracycline, erythromycin, or moxifloxacin. One strain of *Peptostreptococcus anaerobius* (identification confirmed by 16S gene sequencing) had an ampicillin MIC of >8 $\mu\text{g/ml}$ (beta-lactamase negative) and a piperacillin-tazobactam MIC of 16 $\mu\text{g/ml}$ but was susceptible to TD-1792 at an MIC of 0.25 $\mu\text{g/ml}$.

Actinomyces and *Propionibacterium* species were highly susceptible to TD-1792, with MIC_{90} s of ≤ 0.125 $\mu\text{g/ml}$, similar to those for ampicillin, to which these organisms were all susceptible at 0.25 $\mu\text{g/ml}$.

TD-1792 was the most active agent tested against all 34 *Corynebacterium* species examined in this study, with all organisms, including multidrug-resistant strains, susceptible at ≤ 0.25 $\mu\text{g/ml}$. Vancomycin, daptomycin, and linezolid were also consistently active against all strains, but the beta-lactams showed variable activity, with resistance noted in *C. jeikeium*, *C. tuberculostearicum*, and *C. urealyticum*.

TD-1792 showed poor activity against most Gram-negative anaerobes, including *Bacteroides* group species, *Prevotella* spp., *Bilophila wadsworthia*, *Sutterella wadsworthensis*, and *Desulfovibrio* species. Similar to vancomycin, TD-1792 showed good to moderate activity against *Porphyromonas* species (MIC_{90} , 1 $\mu\text{g/ml}$) and *Fusobacterium* species (MIC_{90} , 4 $\mu\text{g/ml}$).

Quality control strains were tested six times against TD-1792. The result for *Staphylococcus aureus* (ATCC 29213) was 0.03 $\mu\text{g/ml}$, and *Clostridium difficile* (ATCC 700057) had a range of 0.5 to 1.0 $\mu\text{g/ml}$. The comparator agents had values within their accepted ranges (6, 7).

TD-1792 is a potent new agent active *in vitro* against a wide spectrum of Gram-positive anaerobes, especially more resistant species of clostridia such as *C. innocuum* and *C. ramosum*. TD-1792 was active *in vitro* against only some Gram-negative anaerobic bacteria, such as *Porphyromonas* and *Fusobacterium* species. It shows promise as a valuable addition to our armamentarium against pathogenic Gram-positive bacteria, yet it does not affect most Gram-negative anaerobic organisms in the intestinal microbiome. TD-1792 warrants further clinical evaluation.

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