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Activity of Ceftolozane-Tazobactam against a Broad Spectrum of Recent Clinical Anaerobic Isolates

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We evaluated *in vitro* activity of ceftolozane-tazobactam (TOL-TAZ), formerly CXA-201, against recent clinical anaerobic isolates with emphasis on the *Bacteroides fragilis* group. Ceftolozane-tazobactam showed good activity against *B. fragilis* species and intermediate to limited activity against other species of *Bacteroides*. Ceftolozane-tazobactam showed very good activity against *Prevotella* spp., *Fusobacterium* spp., and *Propionibacterium* spp., varying activities against Gram-positive cocci, and limited activity against *Clostridium* spp.

Ceftolozane-tazobactam is a novel antibacterial with activity against *Pseudomonas aeruginosa*, including drug-resistant strains, and other common Gram-negative pathogens, including most extended-spectrum beta-lactamase (ESBL)-producing enterobacteriaceae (1–5; D. R. Snydman, N. V. Jacobus, and L. A. McDermott presented at the 22nd European Congress of Clinical Microbiology and Infectious Diseases, London, England, abstr P1445, 2012). Ceftozolane exerts its bactericidal activity by inhibiting essential penicillin-binding proteins (PBP), resulting in inhibition of cell wall synthesis and subsequent cell death. Tazobactam is a potent β-lactamase inhibitor of most common class A and C β-lactamases. It binds covalently to chromosomally and plasmid-mediated bacterial β-lactamases to broaden the coverage of ceftolozane-tazobactam to include β-lactamase-producing Gram-negative organisms.

Tazobactam, a well-established β-lactamase inhibitor that has been combined with piperacillin, has proven to have excellent activity against most of the β-lactamases produced by the *Bacteroides fragilis* group of anaerobes (6–8). The purpose of this study was to evaluate the *in vitro* activities of ceftolozane-tazobactam against a large number of anaerobic pathogens, with emphasis on its activities against *B. fragilis* and related species.

(This study was presented in part at the European Congress on Clinical Microbiology and Infectious Diseases, London, England, 31 March to 3 April 2012.)

Included in the study were 605 recent clinical Gram-positive and Gram-negative anaerobic pathogens. Among the Gram-negative pathogens, 466 were *Bacteroides fragilis* group isolates, including strains with known resistance against some of the comparator agents tested. Also among the Gram-negative pathogens were 33 *Prevotella* spp. and 12 *Fusobacterium* spp. The 94 anaerobic Gram-positive pathogens included 54 *Clostridium* spp., 31 anaerobic cocci, and 9 *Propionibacterium* spp. All isolates were collected between 2010 and 2012. The *B. fragilis* group isolates were referred by 8 medical centers throughout the United States (6, 7). All other isolates were from patients from Tufts Medical Center, Boston, MA.

The MICs of the isolates were determined using agar dilution following Clinical and Laboratory Standards Institute (CLSI) recommendations (9). The susceptibilities of the isolates to ceftolozane, ceftolozane-tazobactam, ampicillin-sulbactam, piperacillin-tazobactam, imipenem, meropenem, tigecycline, moxifloxacin, clindamycin, linezolid, and metronidazole were tested. Vancomycin was added to the test panel when anaerobic Gram-positive isolates were tested, and ertapenem was added to the test panel when *B. fragilis* group isolates were tested. The following ATCC reference organisms were included in quality control (QC) testing: *Bacteroides fragilis* ATCC 25285, *Bacteroides thetaiotaomicron* ATCC 29741, *Clostridium difficile* ATCC 700057, *Eubacterium lentum* ATCC 43055, and *Staphylococcus aureus* ATCC 25923 (used for QC testing for vancomycin). CLSI QC ranges were applied to the results of the QC testing (2).

Table 1 shows the cumulative percentages and MIC distributions of the *B. fragilis* group isolates. Ceftozolane alone exhibited very poor activities against all the species of the *B. fragilis* group: the highest concentration of ceftolozane used in the test, 256 μg/ml, failed to inhibit most of the *B. fragilis* group isolates. The addition of 4 μg/ml of tazobactam to ceftolozane resulted in a significant reduction in the MIC_{90} for all the species of the *B. fragilis* group. The greatest reduction was observed against *B. fragilis*. The MIC_{90} for ceftolozane alone was ≥256 μg/ml, compared to 4 μg/ml for ceftolozane-tazobactam. For most of the other species, the MIC_{90} for ceftolozane-tazobactam was 32 μg/ml. Resistant isolates from all species also showed elevated MICs to ceftolozane-tazobactam. Approximately 10% of the *B. fragilis* group isolates showed no synergistic effect of the addition of tazobactam. This lack of effect did not appear to be species associated (data not shown).

Table 2 shows the comparative activities of ceftolozane-tazobactam and the other agents against the 605 anaerobic isolates tested. The combination was very active against other Gram-negative anaerobes included in the study, *Fusobacterium* spp. and *Prevotella* spp. All 12 isolates of *Fusobacterium* spp. were inhibited at a concentration of 0.25 μg/ml or less of ceftolozane-tazobactam, while all 33 *Prevotella* spp. isolates were inhibited at a concentration of 4 μg/ml or less of ceftolozane-tazobactam.

The activity of ceftolozane-tazobactam varied against the

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TABLE 1 Cumulative percentages and MIC distributions for ceftolozane and ceftolozane-tazobactam against species of the *B. fragilis* group

Species (n[a])	Antibiotic	Cumulative % (no.) of isolates inhibited at MIC (μg/ml) of[d]:											
		≤0.125	0.25	0.5	1	2	4	8	16	32	64	128	≥256
Bacteroides caccae (21)	Ceftolozane	4.8 (1)	4.8 (0)	4.8 (0)	4.8 (0)	4.8 (0)	23.8 (4)	23.8 (0)	28.6 (1)	42.9 (3)	52.4 (2)	66.7 (3)	100 (7)
	TOL-TAZ	14.3 (3)	52.4 (8)	52.4 (0)	57.1 (1)	66.7 (2)	76.2 (2)	85.7 (2)	100 (3)				
Parabacteroides distasonis (25)	Ceftolozane							4 (1)	16 (3)	28 (3)	36 (2)	44 (2)	100 (14)
	TOL-TAZ	12 (3)	16 (1)	24 (2)	24 (0)	28 (1)	40 (3)	48 (2)	80 (8)	92 (3)	96 (1)	96 (0)	100 (1)
Bacteroides fragilis (244)	Ceftolozane	0.8 (2)	1.2 (1)	1.2 (0)	1.6 (1)	2.5 (2)	4.5 (5)	10.7 (15)	18.4 (19)	32.4 (34)	51.6 (47)	65.2 (33)	100 (85)
	TOL-TAZ	18.9 (46)	34 (37)	48.8 (36)	62.3 (33)	79.5 (42)	91.8 (30)	96.7 (12)	98 (3)	98.4 (1)	98.4 (0)	98.8 (1)	100 (3)
Bacteroides ovatus (32)	Ceftolozane			3.1 (1)	6.2 (1)	6.2 (0)	9.4 (1)	9.4 (0)	12.5 (1)	15.6 (1)	31.3 (5)	43.8 (4)	100 (18)
	TOL-TAZ	9.4 (3)	37.5 (9)	40.6 (1)	40.6 (0)	50 (3)	65.6 (5)	81.3 (5)	87.5 (2)	96.9 (3)	96.9 (0)	96.9 (0)	100 (1)
Bacteroides thetaiotaomicron (86)	Ceftolozane		1.2 (1)	1.2 (0)	1.2 (0)	1.2 (0)	3.5 (2)	9.3 (5)	12.8 (3)	22.1 (8)	29.1 (6)	44.2 (13)	100(48)
	TOL-TAZ		30.2 (26)	34.9 (4)	40.7 (5)	43 (2)	52.3 (8)	65.1 (11)	77.9 (11)	93 (13)	96.5 (3)	100 (3)	
Bacteroides uniformis (18)	Ceftolozane			5.6 (1)	5.6 (0)	5.6 (0)	11.1 (1)	27.8 (3)	27.8 (0)	33.3 (1)	61.1 (5)	72.2 (2)	100 (5)
	TOL-TAZ	11.1 (2)	27.8 (3)	27.8 (0)	33.3 (1)	50 (3)	50 (0)	72.2 (4)	94.4 (4)	100 (1)			
Bacteroides vulgatus (28)	Ceftolozane		3.6 (1)	3.6 (0)	7.1 (1)	10.7 (1)	10.7 (0)	14.3 (1)	25 (3)	35.7 (3)	42.9 (2)	64.3 (6)	100 (10)
	TOL-TAZ	21.4 (6)	25 (1)	32.1 (2)	35.7 (1)	39.3 (1)	60.7 (6)	67.9 (2)	89.3 (6)	96.4 (2)	100 (1)		
Other[b] (12)	Ceftolozane	8.3 (1)	8.3 (0)	8.3 (0)	16.7 (1)	16.7 (0)	33.3 (2)	50 (2)	66.7 (2)	66.7 (0)	66.7 (0)	83.3 (2)	100 (2)
	TOL-TAZ	16.7 (2)	50 (2)	58.3 (3)	58.3 (0)	58.3 (0)	83.3 (3)	91.7 (1)	91.7 (0)	91.7 (0)	91.7 (0)	100 (1)	

[a] n, no. of isolates. *Bacteroides thetaiota.*, *Bacteroides thetaiotaomicron*.

[b] Included in this group are isolates of the following species: 2 of *Bacteroides dorei*, 4 of *Parabacteroides goldsteinii*, 2 of *Bacteroides intestinalis*, 1 of *Parabacteroides johnsonii*, 1 of *Parabacteroides merdae*, 1 of *Bacteroides stercoris*, and 1 not identified to the species level.

[c] TOL-TAZ, ceftolozane-tazobactam.

[d] Shaded areas indicate MIC_{90}s.

TABLE 2 Activities of ceftolozane, ceftozolane-tazobactam, and comparative agents against anaerobic isolates

Species or group (n^a)	Antibiotic	MIC (μg/ml)			% Res[b]
		Range	50%	90%	
Bacteroides caccae (21)	Ceftolozane	≤0.125–≥256	64	≥256	NA
	Ceftolozane-tazobactam	≤0.125–16	0.25	16	NA
	Ampicillin-sulbactam	≤0.5–8	1	4	0
	Piperacillin-tazobactam	≤0.5–16	≤0.5	16	0
	Moxifloxacin	≤0.5–>16	2	>16	33.3
	Linezolid	≤0.5–8	1	2	4.8
	Tigecycline	≤0.06–16	0.5	4	4.8
	Imipenem	≤0.125–0.5	≤0.125	0.25	0
	Meropenem	≤0.125–8	0.25	2	0
	Ertapenem	≤0.125–2	0.25	2	0
	Clindamycin	≤0.5–>128	≤0.5	>128	19.0
	Metronidazole	1–2	1	2	0
Parabacteroides distasonis (25)	Ceftolozane	8–≥256	≥256	≥256	NA
	Ceftolozane-tazobactam	≤0.125–16	16	32	NA
	Ampicillin-sulbactam	1–128	8	32	16
	Piperacillin-tazobactam	≤0.5–64	2	8	0
	Moxifloxacin	≤0.5–>16	2	8	20
	Linezolid	≤0.5–8	2	4	4
	Tigecycline	0.5–16	2	4	4
	Imipenem	≤0.125–8	0.25	1	0
	Meropenem	≤0.125–2	0.25	1	0
	Ertapenem	≤0.125–8	0.5	4	0
	Clindamycin	≤0.5–>128	16	>128	44
	Metronidazole	1–2	1	2	0
Bacteroides fragilis (244)	Ceftolozane	≤0.125–≥256	64	≥256	NA
	Ceftolozane-tazobactam	≤0.125–≥256	1	4	NA
	Ampicillin-sulbactam	≤0.5–≥256	2	8	1.1
	Piperacillin-tazobactam	≤0.5–≥256	≤0.5	2	0.6
	Moxifloxacin	≤0.5–>16	1	8	8.8
	Linezolid	≤0.5–4	1	2	0
	Tigecycline	≤0.06–16	≤0.5	2	0.2
	Imipenem	≤0.125–16	≤0.125	0.5	0.6
	Meropenem	≤0.125–16	≤0.125	0.5	1.3
	Ertapenem	≤0.125–16	0.25	1	1.3
	Clindamycin	≤0.5–>128	≤0.5	>128	10.5
	Metronidazole	1–2	1	2	0
Bacteroides ovatus (32)	Ceftolozane	1–≥256	≥256	≥256	NA
	Ceftolozane-tazobactam	≤0.125–≥256	4	32	NA
	Ampicillin-sulbactam	≤0.5–8	1	8	0
	Piperacillin-tazobactam	≤0.5–32	1	8	0
	Moxifloxacin	≤0.5–>16	4	16	43.8
	Linezolid	≤0.5–2	1	2	0
	Tigecycline	≤0.06–4	0.25	2	0
	Imipenem	≤0.125–2	≤0.125	0.25	0
	Meropenem	≤0.125–8	≤0.125	0.5	0
	Ertapenem	≤0.125–8	0.5	2	0
	Clindamycin	≤0.5–128	1	128	15.6
	Metronidazole	1–2	1	2	0
Bacteroides thetaiotaomicron (86)	Ceftolozane	0.25–≥256	≥256	≥256	NA
	Ceftolozane-tazobactam	≤0.125–128	4	32	NA
	Ampicillin-sulbactam	≤0.5–64	1	8	2.3
	Piperacillin-tazobactam	≤0.5–32	1	8	0
	Moxifloxacin	≤0.5–>16	2	>16	32.6
	Linezolid	≤0.5–16	1	2	2.3
	Tigecycline	≤0.06–16	0.25	2	1.2
	Imipenem	≤0.125–4	≤0.125	0.5	0

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TABLE 2 (Continued)

Species or group (n^a)	Antibiotic	MIC (μg/ml)			% Res[b]
		Range	50%	90%	
	Meropenem	≤0.125–4	≤0.125	1	0
	Ertapenem	≤0.125–8	0.25	2	0
	Clindamycin	≤0.5–>128	1	>128	29.1
	Metronidazole	1–2	1	2	0
Bacteroides uniformis (18)	Ceftolozane	0.5–≥256	64	≥256	NA
	Ceftolozane-tazobactam	≤0.125–32	2	16	NA
	Ampicillin-sulbactam	≤0.5–8	1	2	0
	Piperacillin-tazobactam	≤0.5–16	1	2	0
	Moxifloxacin	≤0.5–>16	1	4	11.1
	Linezolid	≤0.5–16	1	2	11.1
	Tigecycline	≤0.06–4	0.125	0.5	0
	Imipenem	≤0.125–0.25	≤0.125	0.25	0
	Meropenem	≤0.125–0.5	≤0.125	0.25	0
	Ertapenem	≤0.125–2	0.25	0.5	0
	Clindamycin	≤0.5–128	1	>128	27.8
	Metronidazole	1–2	1	2	0
Bacteroides vulgatus (28)	Ceftolozane	0.25–≥256	128	≥256	NA
	Ceftolozane-tazobactam	<0.125–≥256	4	32	NA
	Ampicillin-sulbactam	≤0.5–16	4	16	0
	Piperacillin-tazobactam	≤0.5–16	2	8	0
	Moxifloxacin	≤0.5–>16	>16	32	75
	Linezolid	<0.5–4	1	2	0
	Tigecycline	≤0.06–4	0.5	2	0
	Imipenem	≤0.125–0.5	0.25	0.5	0
	Meropenem	≤0.125–1	0.25	0.5	0
	Ertapenem	≤0.125–2	0.5	1	0
	Clindamycin	≤0.5–>128	≤0.5	>128	39.3
	Metronidazole	1–2	1	2	0
Other *Bacteroides*[c] (12)	Ceftolozane	0.25–≥256	8	≥256	NA
	Ceftolozane-tazobactam	≤0.125–128	0.25	8	NA
	Ampicillin-sulbactam	≤0.5–8	0.5	8	0
	Piperacillin-tazobactam	≤0.5–4	0.5	2	0
	Moxifloxacin	≤0.5–>16	≤0.5	8	25
	Linezolid	≤0.5–4	1	2	0
	Tigecycline	≤0.06–8	0.25	2	0
	Imipenem	≤0.125–0.5	≤0.125	0.25	0
	Meropenem	≤0.125–8	0.5	8	0
	Ertapenem	≤0.125–8	0.5	4	0
	Clindamycin	≤0.5–>128	≤0.5	1	0
	Metronidazole	1–2	1	2	0
Prevotella spp. (33)	Ceftolozane	≤0.125–≥256	16	≥256	NA
	Ceftolozane-tazobactam	≤0.125–4	≤0.125	1	NA
	Ampicillin-sulbactam	≤0.5–4	1	4	0
	Piperacillin-tazobactam	≤0.5–4	0.5	2	0
	Moxifloxacin	≤0.5–16	2	8	9.1
	Linezolid	≤0.5–8	2	4	3
	Tigecycline	≤0.06–4	≤0.5	1	0
	Imipenem	All ≤0.125	≤0.125	≤0.125	0
	Meropenem	≤0.125–0.5	≤0.125	0.25	0
	Clindamycin	≤0.5–>128	≤0.5	>128	21.2
	Metronidazole	1–2	1	2	0
Fusobacterium spp. (12)	Ceftolozane	≤0.125–16	≤0.125	16	NA
	Ceftolozane-tazobactam	≤0.125–0.25	≤0.125	0.25	NA
	Ampicillin-sulbactam	≤0.5–1	≤0.5	1	0

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TABLE 2 (Continued)

Species or group (n^a)	Antibiotic	MIC (μg/ml)			% Res[b]
		Range	50%	90%	
	Piperacillin-tazobactam	≤0.5–1	≤0.5	8	0
	Moxifloxacin	≤0.5–4	≤0.5	4	0
	Linezolid	≤0.5–2	≤0.5	2	0
	Tigecycline	≤0.06–0.125	≤0.06	0.125	0
	Imipenem	All ≤0.125	≤0.125	≤0.125	0
	Meropenem	All ≤0.125	≤0.125	≤0.125	0
	Clindamycin	≤0.5–2	≤0.5	2	0
	Metronidazole	All 1	1	1	0
Clostridium difficile (30)	Ceftolozane	32–≥256	≥256	≥256	NA
	Ceftolozane-tazobactam	0.25–≥256	≥256	≥256	NA
	Ampicillin-sulbactam	≤0.5–16	1	4	0
	Piperacillin-tazobactam	≤0.5–128	8	16	3.3
	Moxifloxacin	≤0.5–>16	2	>16	43.3
	Linezolid	≤0.5–4	1	2	0
	Tigecycline	≤0.06–4	≤0.06	1	0
	Imipenem	≤0.125–16	4	8	3.3
	Meropenem	≤0.125–8	2	2	0
	Vancomycin	≤0.125–8	2	4	NA
	Clindamycin	1–16	2	16	23.3
	Metronidazole	1–4	2	4	0
Clostridium perfringens (11)	Ceftolozane	0.5–64	1	64	NA
	Ceftolozane-tazobactam	≤0.125–32	0.25	32	NA
	Ampicillin-sulbactam	≤0.5–1	≤0.5	1	0
	Piperacillin-tazobactam	≤0.5–2	≤0.5	2	0
	Moxifloxacin	≤0.5–4	1	4	0
	Linezolid	1–4	2	4	0
	Tigecycline	0.125–8	0.5	8	0
	Imipenem	≤0.125–0.25	≤0.125	0.25	0
	Meropenem	All ≤0.125	≤0.125	≤0.125	0
	Vancomycin	1–2	1	2	NA
	Clindamycin	≤0.5–4	2	4	0
	Metronidazole	1–2	1	2	0
Clostridium spp.[d] (13)	Ceftolozane	0.5–≥256	≥ 256	≥256	NA
	Ceftolozane-tazobactam	≤0.125–≥256	16	≥256	NA
	Ampicillin-sulbactam	≤0.5–4	≤0.5	1	0
	Piperacillin-tazobactam	≤0.5–4	2	4	0
	Moxifloxacin	≤0.5–4	1	2	0
	Linezolid	≤0.5–4	2	4	0
	Tigecycline	0.125–4	2	4	0
	Imipenem	≤0.125–4	1	4	0
	Meropenem	≤0.125–2	0.25	2	0
	Vancomycin	≤0.125–4	1	4	NA
	Clindamycin	1–16	2	4	7.7
	Metronidazole	1–4	2	4	0
Anaerobic Gram$^+$ cocci (31)	Ceftolozane	≤0.125–≥256	4	16	NA
	Ceftolozane-tazobactam	≤0.125–64	2	8	NA
	Ampicillin-sulbactam	≤0.5–2	≤0.5	1	0
	Piperacillin-tazobactam	≤0.5–16	≤0.5	2	0
	Moxifloxacin	≤0.5–16	≤0.5	16	9.7
	Linezolid	≤0.5–4	1	2	0
	Tigecycline	≤0.06–1	0.125	0.5	0
	Imipenem	≤0.125–4	≤0.125	0.25	0
	Meropenem	≤0.125–0.25	≤0.125	≤0.125	0
	Vancomycin	≤0.125–2	0.5	2	NA
	Clindamycin	≤0.5–16	≤0.5	2	3.2
	Metronidazole	1–16	1	2	0

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TABLE 2 (Continued)

Species or group (n^a)	Antibiotic	MIC (μg/ml)			% Res[b]
		Range	50%	90%	
Propionibacterium[e] spp. (9)	Ceftolozane	≤0.125–16	0.5		NA
	Ceftolozane-tazobactam	All ≤0.125	≤0.125		NA
	Ampicillin-sulbactam	All ≤0.5	≤0.5		0
	Piperacillin-tazobactam	All ≤0.5	≤0.5		0
	Moxifloxacin	All 1	1		0
	Linezolid	All 1	1		0
	Tigecycline	≤0.06–0.5	≤0.06		0
	Imipenem	All ≤0.125	≤0.125		0
	Meropenem	≤0.125–0.25	≤0.125		0
	Vancomycin	0.25–1	0.5		0
	Clindamycin	≤0.5–16	≤0.5		22.2
	Metronidazole	All >32	>32		100

[a] *n*, no. of isolates.
[b] Percent resistance calculated using CLSI recommendations for most antimicrobial agents. For resistance breakpoints, refer to reference 9, CLSI document M11-A7. For tigecycline, the breakpoint for resistance of 16 μg/ml is the FDA recommendation. Please see reference 10, tigecycline package insert. NA, not applicable; there are no established breakpoints for these agents.
[c] Includes isolates of the following *Bacteroides* species: 2 of *Bacteroides dorei*, 4 of *Parabacteroides goldsteinii*, 2 of *Bacteroides intestinalis*, 1 of *Parabacteroides johnsonii*, 1 of *Parabacteroides merdae*, 1 of *Bacteroides stercoris*, and 1 not identified to the species level.
[d] Includes isolates of the following species: 3 of *C. septicum*, 1 of *C. subterminale*, 1 of *C. tertium*, 1 of *C. cadaveris*, 1 of *C. clostridioforme*, and 6 of *Clostridium* spp.
[e] The number of *Propionibacterium* species isolates is less than 10; therefore, the MIC_{90} was not calculated.

Gram-positive anaerobic species. The combination showed excellent activity against the 9 *Propionibacterium* spp. (all isolates inhibited by ≤0.125 μg/ml), intermediate activity against anaerobic Gram-positive cocci (MIC_{90}, 8 μg/ml), and very limited activity against *Clostridium* spp. (MIC_{90} range, 64 to >256 μg/ml).

This study demonstrates that the addition of tazobactam to ceftolozane enhances its activity against *Bacteroides* species. However, the enhanced activity is mostly limited to *B. fragilis* and to non-*Bacteroides* Gram-negative anaerobes. This might have clinical significance, since *B. fragilis* is the most commonly isolated species in intra-abdominal infections (6, 7). Ceftolozane-tazobactam will likely need to be used in combination with more potent antianaerobic agents for the management of intra-abdominal infections. For head and neck infections or aspiration pneumonia, the combination of ceftolozane and tazobactam may be sufficient, pending results from clinical trials.

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