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Characteristics and Outcomes of Complicated Intra-abdominal Infections Involving *Pseudomonas aeruginosa* from a Randomized, Double-Blind, Phase 3 Ceftolozane-Tazobactam Study

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Ceftolozane-tazobactam is active against Gram-negative pathogens, including multidrug-resistant *Pseudomonas aeruginosa*. In a subgroup analysis of patients with complicated intra-abdominal infections (cIAIs) involving *P. aeruginosa* from a phase 3 program, ceftolozane-tazobactam demonstrated potent *in vitro* activity against *P. aeruginosa*. Clinical cure in the microbiologically evaluable population was 100% (26/26) for ceftolozane-tazobactam plus metronidazole and 93.1% (27/29) for meropenem. These findings support the use of ceftolozane-tazobactam in the management of cIAI when *P. aeruginosa* is suspected or confirmed. (This study has been registered at ClinicalTrials.gov under registration no. NCT01445665 and NCT01445678.)

Complicated intra-abdominal infections (cIAIs) are caused by Gram-negative bacteria, with *Enterobacteriaceae* being the most common pathogen. *Pseudomonas aeruginosa* is the third-most-common Gram-negative bacteria in cIAI (1), and increasing rates of *P. aeruginosa* resistance are a global concern (2, 3).

Ceftolozane-tazobactam, in combination with metronidazole, is approved for the treatment of cIAI (4). Ceftolozane-tazobactam has potent activity against many drug-resistant Gram-negative pathogens, including most extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae* (5, 6), and is minimally affected by common *P. aeruginosa* resistance mechanisms (7). Compared with approved β-lactam antibiotics, including meropenem and piperacillin-tazobactam, ceftolozane-tazobactam displays more potent *in vitro* activity against *P. aeruginosa* (8).

The Assessment of the Safety Profile and Efficacy of Ceftolozane/Tazobactam in Complicated Intra-Abdominal Infections (ASPECT-cIAI) study was a global phase 3 program that demonstrated the efficacy of ceftolozane-tazobactam plus metronidazole to be similar to that of meropenem in patients with cIAI (NCT01445665 and NCT01445678) (9). This analysis was conducted to determine the characteristics and clinical outcomes of the subgroup of patients with *P. aeruginosa* infection.

(Part of this research was presented as poster 251 at IDWeek, the annual meeting of the Infectious Diseases Society of America [IDSA], the Society for Healthcare Epidemiology of America [SHEA], the HIV Medicine Association [HIVMA], and the Pediatric Infectious Diseases Society [PIDS], 8 to 12 October 2014, Philadelphia, PA.)

In ASPECT-cIAI, patients (age, ≥18 years) with cIAI were randomly assigned 1:1 to receive intravenous ceftolozane-tazobactam (1.5 g containing 1,000 mg ceftolozane and 500 mg tazobactam) plus metronidazole (500 mg) every 8 h or intravenous meropenem (1 g every 8 h) plus placebo for 4 to 14 days. Efficacy was assessed at the test-of-cure visit 24 to 32 days after initiation of the study drug. Clinical cure was defined as the resolution of or significant improvement in signs and symptoms of the index infection, such that no additional antibacterial therapy or intervention was necessary. Descriptive statistics were used to compare baseline characteristics (microbiological intent-to-treat [MITT] population) and clinical outcomes (microbiologically evaluable [ME] population) of patients with and without *P. aeruginosa* infection. Descriptions of inclusion/exclusion criteria and study design were published previously (9).

MIC cutoffs for susceptibility to ceftolozane-tazobactam and meropenem were based on Clinical and Laboratory Standards Institute (CLSI) definitions (10). Multidrug resistance (MDR) in *P. aeruginosa* was based on CLSI breakpoints and defined as nonsusceptibility to ≥3 drug classes known to be active against *P. aeruginosa*. *P. aeruginosa* isolates were screened for AmpC overexpression.

In the MITT population, 8.9% (72/806) of patients had *P. aeruginosa* infection at baseline; 4 patients had *P. aeruginosa* as the only infecting pathogen. Baseline demographic characteristics were similar between patients with and those without *P. aeruginosa* infection (Table 1). *P. aeruginosa* infection was more frequent in North America (17.6% [9/51]) than in Europe (7.9% [50/635]) and more commonly isolated in patients with colonic (14.4% [7/118]) or appendiceal (11.2% [43/384]) infections. In patients with *P. aeruginosa* infection, 65.3% (47/72) received previous antibacterial therapy, compared with 56.8% (417/734) of patients without *P. aeruginosa* infection. Previous therapies included metronidazole (41.7%), ceftriaxone (12.5%), and cefotaxime (8.3%); mean duration of therapy (7.8 days) was the same

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TABLE 1 Baseline demographics of all patients in the ASPECT-cIAI trial (microbiological intent-to-treat population)

Characteristic	*P. aeruginosa* at baseline ($n = 72$)	No *P. aeruginosa* at baseline ($n = 734$)	Total ($n = 806$)
Sex, male (*n* [%])	48 (66.7)	418 (56.9)	446 (57.8)
Race, white (*n* [%])	63 (87.5)	692 (94.3)	755 (93.7)
Mean age (SD) (yr)	49.5 (19.3)	50.7 (17.4)	50.6 (17.5)
≥75 yr (*n* [%])	8 (11.1)	75 (10.2)	83 (10.3)
Mean body mass index (SD) (kg/m^2)	27.1 (6.3)	26.9 (5.3)	26.9 (5.4)
Baseline APACHE II score category (*n* [%])[a]			
<10	61 (84.7)	596 (81.2)	657 (81.5)
≥10	11 (15.3)	137 (18.7)	148 (18.4)
Creatinine clearance (ml/min) (*n* [%])			
Normal (≥80)	47 (65.3)	516 (70.3)	563 (69.9)
Mild renal impairment (>50 to <80)	24 (33.3)	183 (24.9)	207 (25.7)
Moderate renal impairment (≥30 to ≤50)	1 (1.4)	35 (4.8)	36 (4.5)
Geographic origin (*n* [%])			
Europe	50 (69.4)	585 (79.7)	635 (78.8)
North America	9 (12.5)	42 (5.7)	51 (6.3)
South America	6 (8.3)	75 (10.2)	81 (10.0)
Rest of world	7 (9.7)	32 (4.4)	39 (4.8)
Anatomic site of infection (*n* [%])			
Appendix	43 (59.7)	341 (46.5)	384 (47.6)
Biliary cholecystitis/cholangitis	5 (6.9)	138 (18.8)	143 (17.7)
Stomach/duodenum	4 (5.6)	75 (10.2)	79 (9.8)
Colon	17 (23.6)	101 (13.8)	118 (14.6)
Small bowel	1 (1.4)	41 (5.6)	42 (5.2)
Parenchymal (liver)	1 (1.4)	32 (4.4)	33 (4.1)
Parenchymal (spleen)	0	4 (0.5)	4 (0.5)
Other	1 (1.4)	15 (2.0)	16 (2.0)

[a] Data missing for 1 patient. APACHE II, Acute Physiology and Chronic Health Evaluation II.

for patients with and those without *P. aeruginosa* infection. In total, 8.9% (4/5) of patients for whom previous antibacterial therapy was ineffective (amoxicillin-clavulanic acid and ertapenem; cefotaxime, metronidazole, and piperacillin-tazobactam; metronidazole and cefuroxime axetil; and metronidazole, ceftriaxone sodium, and cefuroxime axetil) had *P. aeruginosa* infection.

Most *P. aeruginosa* (97.2% [70/72]) and non-*P. aeruginosa* (92.9% [682/734]) infections were community acquired, and *P. aeruginosa* was more likely to be isolated as part of a polymicrobial infection (94.4% [68/72]). All three cases of concurrent bacteremia in patients with *P. aeruginosa* occurred with polymicrobial infections; bacteremia was a result of *Propionibacterium acnes*, *Eggerthella lenta*, and *Enterococcus faecalis* infection, and all patients were deemed to be clinically cured.

Both ceftolozane-tazobactam and meropenem were highly active *in vitro* against *P. aeruginosa*, with an MIC required to inhibit the growth of 90% of isolates (MIC_{90}) of 2 μg/ml for ceftolozane-tazobactam and 4 μg/ml for meropenem. Ceftolozane-tazobactam was the most potent agent tested; 97.1% of isolates were inhibited at an MIC of ≤4 μg/ml, whereas susceptibility to meropenem was 89.9% (Fig. 1A). Based on MIC_{90} values, ceftolozane-tazobactam (MIC_{90}, 2 μg/ml) was 32-fold more active than piperacillin-tazobactam (MIC_{90}, 64 μg/ml) and 8-fold more active than ceftazidime, cefepime, aztreonam, or gentamicin (MIC_{90}, 16 μg/ml for each).

In the MITT population, 15.7% (11/70) of molecularly characterized *P. aeruginosa* isolates overexpressed AmpC; the MIC range was 0.5 to 16 μg/ml for ceftolozane-tazobactam and 0.25 to 8 μg/ml for meropenem. Three patients in the meropenem group had MDR *P. aeruginosa*; the MIC range was 4 to 16 μg/ml for ceftolozane-tazobactam and 2 to 4 μg/ml for meropenem. In the ME population, 10 patients had *P. aeruginosa* infection that overexpressed AmpC, and 3 patients had MDR *P. aeruginosa* (Table 2).

Clinical cure rates in the ME population for patients with and without *P. aeruginosa* infection at baseline (regardless of pathogen susceptibility to study treatment) are summarized in Fig. 1B. For two patients with *P. aeruginosa* in the meropenem group, treatment was ineffective because of persistent/recurrent abdominal infection that necessitated additional intervention. Both treatments were 100% effective against overexpressed AmpC and MDR *P. aeruginosa* isolates (Table 2).

Understanding the risk factors associated with *P. aeruginosa* involvement in cIAI is important for making empirical treatment decisions (11, 12). In this study, nearly 10% of patients had *P. aeruginosa* infection, consistent with the findings in previous studies (13–16), and previous antibacterial exposure was more frequent among those with *P. aeruginosa*. Prophylactic metronidazole and third-generation cephalosporins were common previous treatments, which potentially predisposed patients to *P. aeruginosa* infection.

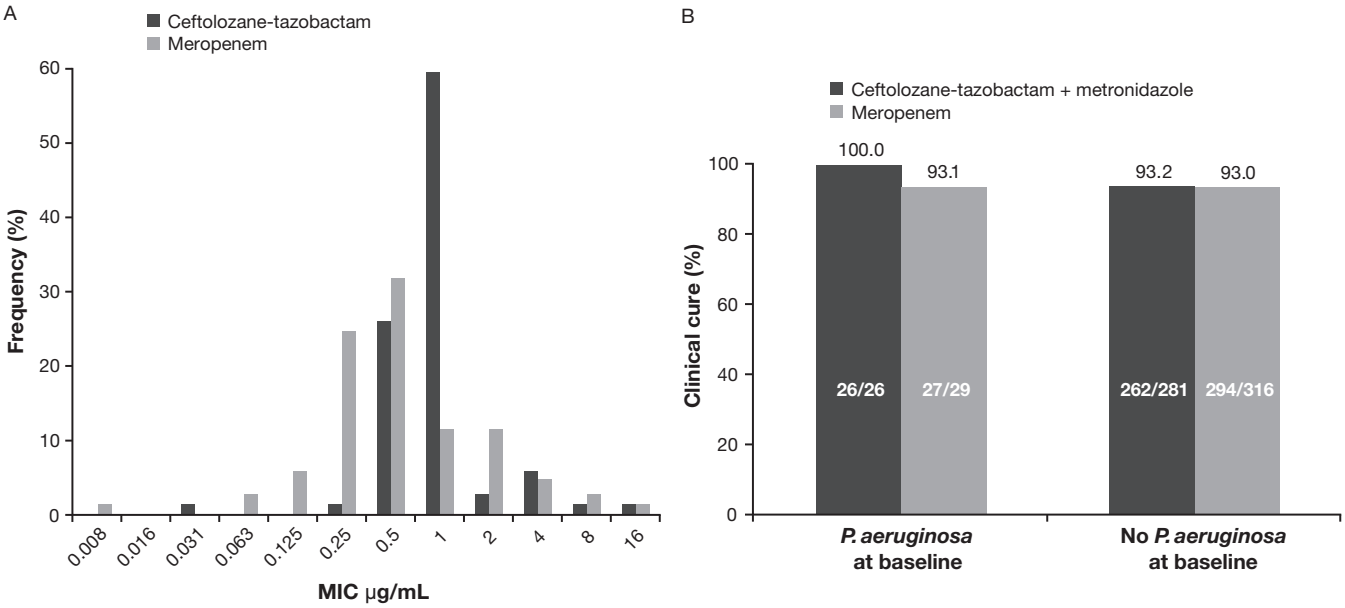

FIG 1 MIC distribution and clinical outcomes with ceftolozane-tazobactam and meropenem. (A) Distribution of ceftolozane-tazobactam and meropenem MICs for 69 *Pseudomonas aeruginosa* isolates identified at the screening visit (microbiological intent-to-treat population). (B) Clinical cure rate at the test-of-cure visit for patients with and without baseline *P. aeruginosa* infection, by treatment group (microbiologically evaluable population, which includes patients with pathogens at baseline who were susceptible or resistant to study drug).

All patients in the ME population with *P. aeruginosa* infection had a 100% clinical cure rate with ceftolozane-tazobactam plus metronidazole. In this study of primarily community-acquired cIAIs, the prevalence of MDR *P. aeruginosa* was low; nevertheless, ceftolozane-tazobactam had potent *in vitro* activity against *P. aeruginosa* (MIC_{90}, 2 μg/ml). Because of the small number of patients in this nonrandomized subgroup analysis, the summary of data might have been subject to bias.

Ceftolozane-tazobactam plus metronidazole was effective in AmpC-overexpressing strains of *P. aeruginosa*, consistent with *in vitro* studies that have shown ceftolozane's stability against *P. aeruginosa* resistance mechanisms, including hydrolysis by AmpC enzymes, upregulation of efflux pumps, and decreases in porin expression (7, 17, 18).

Ceftolozane-tazobactam has been shown to be active against strains of *P. aeruginosa* that are resistant to carbapenems, piperacillin-tazobactam, cephalosporins, fluoroquinolones, and aminoglycosides, including the majority of MDR isolates (17, 19, 20), with the exception of metallo-β-lactamases. The ASPECT-cIAI findings suggest that ceftolozane-tazobactam will be an important

TABLE 2 *In vitro* activity of ceftolozane-tazobactam and comparator antibacterials against AmpC-producing and MDR *P. aeruginosa* isolates identified at screening visit (microbiologically evaluable population)

Treatment group	Clinical outcome	MIC (μg/ml)						
		Ceftolozane-tazobactam	Meropenem	Aztreonam	Cefepime	Ceftazidime	Gentamicin	Piperacillin-tazobactam
AmpC producers ($n = 10$)								
Ceftolozane-tazobactam	Cure	0.5	1	4	2	2	1	8
Ceftolozane-tazobactam	Cure	1	0.5	8	2	4	2	16
Ceftolozane-tazobactam	Cure	1	1	8	4	4	2	8
Ceftolozane-tazobactam	Cure	2	2	8	16	16	>16	64
Ceftolozane-tazobactam	Cure	1	4	4	4	4	2	8
Meropenem[a]	Cure	4	2	16	16	16	>16	128
Meropenem	Cure	1	0.5	4	4	4	1	8
Meropenem	Cure	1	0.25	0.5	2	1	2	≤0.25
Meropenem	Cure	16	2	32	32	>32	>16	>128
Meropenem	Cure	4	4	>32	32	>32	16	>128
MDR[b] ($n = 3$)								
Meropenem[a]	Cure	4	2	16	16	8	>16	128
Meropenem	Cure	16	2	32	32	>32	>16	>128
Meropenem	Cure	4	4	>32	32	>32	16	>128

[a] Isolate was positive for AmpC and MDR.
[b] MDR was based on CLSI breakpoints and defined as nonsusceptiblity to ≥3 drug classes that are known to be active against *P. aeruginosa*.

addition to the available antibacterials used in the treatment of cIAIs, especially when *P. aeruginosa* is implicated.

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We and employees of the study sponsor were involved in the study design, data collection, and interpretation and in the decision to submit the work for publication.

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