Ceftolozane/Tazobactam Plus Metronidazole for Complicated Intra-abdominal Infections in an Era of Multidrug Resistance: Results From a Randomized, Double-Blind, Phase 3 Trial (ASPECT-cIAI)

Joseph Solomkin,[1] Ellie Hershberger,[2] Benjamin Miller,[2] Myra Popejoy,[2] Ian Friedland,[2,a] Judith Steenbergen,[2] Minjung Yoon,[2] Sylva Collins,[2] Guojun Yuan,[2] Philip S. Barie,[3] and Christian Eckmann[4]

[1]Department of Surgery, University of Cincinnati College of Medicine, Cincinnati, Ohio; [2]Cubist Pharmaceuticals, Lexington, Massachusetts; [3]Departments of Surgery and Medicine, Weill Cornell Medical College, New York, New York; and [4]Department of General, Visceral and Thoracic Surgery, Academic Hospital of Medical University Hannover, Peine, Germany

Background. Increasing antimicrobial resistance among pathogens causing complicated intra-abdominal infections (cIAIs) supports the development of new antimicrobials. Ceftolozane/tazobactam, a novel antimicrobial therapy, is active against multidrug-resistant *Pseudomonas aeruginosa* and most extended-spectrum β-lactamase (ESBL)–producing Enterobacteriaceae.

Methods. ASPECT-cIAI (Assessment of the Safety Profile and Efficacy of Ceftolozane/Tazobactam in Complicated Intra-abdominal Infections) was a prospective, randomized, double-blind trial. Hospitalized patients with cIAI received either ceftolozane/tazobactam (1.5 g) plus metronidazole (500 mg) every 8 hours or meropenem (1 g) every 8 hours intravenously for 4–14 days. The prospectively defined objectives were to demonstrate statistical noninferiority in clinical cure rates at the test-of-cure visit (24–32 days from start of therapy) in the microbiological intent-to-treat (primary) and microbiologically evaluable (secondary) populations using a noninferiority margin of 10%. Microbiological outcomes and safety were also evaluated.

Results. Ceftolozane/tazobactam plus metronidazole was noninferior to meropenem in the primary (83.0% [323/389] vs 87.3% [364/417]; weighted difference, −4.2%; 95% confidence interval [CI], −8.91 to .54) and secondary (94.2% [259/275] vs 94.7% [304/321]; weighted difference, −1.0%; 95% CI, −4.52 to 2.59) endpoints, meeting the prespecified noninferiority margin. In patients with ESBL-producing Enterobacteriaceae, clinical cure rates were 95.8% (23/24) and 88.5% (23/26) in the ceftolozane/tazobactam plus metronidazole and meropenem groups, respectively, and 100% (13/13) and 72.7% (8/11) in patients with CTX-M-14/15 ESBLs. The frequency of adverse events (AEs) was similar in both treatment groups (44.0% vs 42.7%); the most common AEs in either group were nausea and diarrhea.

Conclusions. Treatment with ceftolozane/tazobactam plus metronidazole was noninferior to meropenem in adult patients with cIAI, including infections caused by multidrug-resistant pathogens.

Clinical Trials Registration. NCT01445665 and NCT01445678.

Keywords. complicated intra-abdominal infection; ceftolozane/tazobactam; multidrug resistance; gram-negative bacteria; Enterobacteriaceae.

Complicated intra-abdominal infections (cIAIs) are tissue-invasive infections leading to abscess formation or generalized peritonitis. The management of cIAIs involves operative or percutaneous intervention to obtain surgical control of the source. Nonetheless, patients with cIAIs are at risk of sepsis and mortality [1–4].

Empiric antimicrobial therapy with appropriate agents is an important component of treatment [5, 6]. Initial empiric therapy that is not effective against infecting pathogens increases costs, treatment failure, and death [7–10]. Because of this, cIAIs are an important infection category for evaluation of the efficacy of investigational agents.

The well-recognized appearance of antimicrobial resistance among gram-negative bacteria has stimulated the development of novel agents [11], particularly those targeting Enterobacteriaceae that produce extended-spectrum β-lactamases (ESBLs) [12], which confer resistance to most β-lactam antimicrobial agents [1].

Ceftolozane/tazobactam consists of a novel cephalosporin and an established β-lactamase inhibitor that is being developed to address antimicrobial resistance in serious infections caused by gram-negative pathogens, including cIAI, complicated urinary tract infection/pyelonephritis (cUTI), and ventilated nosocomial pneumonia. In vitro activity of ceftolozane/tazobactam has been confirmed against ESBL-producing Enterobacteriaceae, drug-resistant *Pseudomonas aeruginosa* [13–16], and some *Streptococcus* species [17]. The results from a phase 2 study with ceftolozane/tazobactam in combination with metronidazole in cIAI supported further development for this indication [18].

We now report the results from ASPECT-cIAI (Assessment of the Safety Profile and Efficacy of Ceftolozane/Tazobactam in Complicated Intra-abdominal Infections), a large global phase 3 clinical program that evaluated intravenous ceftolozane/tazobactam plus metronidazole vs meropenem for the treatment of hospitalized adult patients with cIAI.

PATIENTS AND METHODS

Study Design
Two identical multicenter, prospective, randomized, double-blind, placebo-controlled trials were initiated in December 2011 at 196 study centers worldwide (ClinicalTrials.gov identifiers NCT01445665 and NCT01445678).

The trials were designed in compliance with current clinical guidelines and the regulatory requirements of the US Food and Drug Administration (FDA) and the European Medicines Agency, approved by local institutional review boards, and conducted in accordance with the International Conference on Harmonisation/Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. All patients were required to provide written informed consent prior to participation. In 2012, the FDA released a draft guidance providing for a single study pathway for approval of antibiotics in cUTI and cIAI [19]. The sponsor sought and received prospective permission from the relevant regulatory agencies to pool the data from the 2 protocols upon completion to form a single dataset for analysis. Enrollment in the 2 protocols was completed in September 2013, and data were pooled after database lock in each study.

Inclusion Criteria
Patients were to be ≥18 years of age, with clinical evidence of cIAI. Operative or percutaneous drainage of an infectious focus was either planned or had been performed recently (within 24 hours), confirming the presence of cIAI.

Exclusion Criteria
The following exclusions applied: cIAI managed by staged abdominal repair in which the fascia was not closed; low likelihood of adequate source control at surgery; creatinine clearance <30 mL/minute; or use of systemic antimicrobial therapy for IAI for >24 hours prior to the first dose of study drug (unless this treatment failed, defined by the need for additional intervention and persistent signs of ongoing infection with a positive culture of intra-abdominal abscess or peritonitis fluid, despite >48 hours of prior antimicrobial therapy).

Randomization and Treatment
Randomization numbers were computer-generated. Patients were assigned (1:1) by the study site's pharmacist to intravenous ceftolozane/tazobactam 1.5 g (containing 1 g ceftolozane and 500 mg tazobactam) plus metronidazole (500 mg every 8 hours) or intravenous meropenem (1 g every 8 hours) plus placebo for 4–10 days. Treatment could be continued for up to 14 days in patients who had 1 of the following: multiple abscesses; non-appendix-related diffuse peritonitis, failure of prior antimicrobial therapy, or hospital-acquired infection. The dose of ceftolozane/tazobactam was based on data from previous clinical studies [18, 20]. The comparator, meropenem, is recommended by the Surgical Infection Society and the Infectious Diseases Society of America as appropriate first-line empiric therapy for high-risk and severe cIAI, and is prescribed commonly for this indication [5, 6]. In patients with moderate renal impairment (creatinine clearance, 30–50 mL/minute), the ceftolozane/tazobactam dose was reduced to 750 mg every 8 hours and the meropenem dose to 1 g every 12 hours. Placebo saline infusions were used to maintain blinding. Drug assignment was concealed from the patient and all clinical and study staff.

Assessments
At baseline, intra-abdominal specimens were collected from aspirates (collected with a needle or a syringe) for culture of aerobes and anaerobes. Samples were inoculated into aerobic and anaerobic culture bottles, incubated at 35°C–37°C, and transferred to

the microbiology laboratory. Signs and symptoms of the index infection were recorded daily. Blood samples for culture were drawn in patients with hospital-acquired infections, those who had failed prior antimicrobial therapy, and those with signs of severe sepsis [21]. Other baseline assessments included measurement of disease severity, as determined by the Acute Physiology and Chronic Health Evaluation (APACHE) II score; measurements of hematology, chemistry, and coagulation; urinalysis; and estimation of creatinine clearance.

Outcome Assessment

Clinical outcomes were assessed at the end of therapy (within 24 hours of last dose of treatment), the test-of-cure (TOC) visit (24–32 days after start of therapy), and the late follow-up visit (38–45 days after start of therapy). Clinical cure was defined as complete resolution or significant improvement in signs and symptoms of the index infection, such that no additional antimicrobials or interventions were required. Events defining clinical failure included death due to cIAI prior to the TOC visit, persisting or recurrent infection requiring additional intervention, treatment with additional antimicrobials for ongoing symptoms of IAI, and/or surgical site infection [22]. An indeterminate response was recorded when trial data were not available for evaluation of efficacy for any reason, including death unrelated to the index infection, or in extenuating circumstances that precluded classification as cure or failure. Analysis populations are defined in Supplementary Table 1. Patients with missing clinical outcome data or indeterminate responses were considered to have failed treatment in the intent-to-treat (ITT) and microbiological ITT (MITT) analyses, but were excluded from the per-protocol (clinically evaluable [CE] and microbiologically evaluable [ME]) analyses.

Pathogen susceptibility to ceftolozane/tazobactam was defined as a minimum inhibitory concentration (MIC) ≤8 mg/L, intermediate as an MIC of 16 mg/L, and resistant as an MIC ≥32 mg/L. MIC cutoffs for determination of susceptibility to meropenem were based on Clinical Laboratory Standards Institute (CLSI) definitions. Enterobacteriaceae susceptibility was defined as MIC ≤1 mg/L, intermediate as MIC 2 mg/L, and resistant as MIC ≥4 mg/L. For *P. aeruginosa*, the MIC cutoffs were ≤2 mg/L, 4 mg/L, and ≥8 mg/L, respectively [23]. Multidrug resistance in *P. aeruginosa* was based on the CLSI breakpoints and was defined as resistance or nonsusceptibility to ≥3 drug classes that are known to be active against *P. aeruginosa*. Enterobacteriaceae organisms with an ESBL phenotype (predefined criteria: MIC ≥2 mg/L for any cephalosporin, ≥3 dilution change in MIC when an antibiotic was combined with a β-lactamase inhibitor) identified prior to database lock were characterized by JMI Laboratories (North Liberty, Iowa) using a commercial MicroArray System Check-MDR CT101 kit (Checkpoints, Wageningen, the Netherlands). Safety was assessed by

review of adverse events (AEs), vital signs, physical examination findings, and clinical laboratory results.

Source Control Review

All patients with a baseline pathogen and an investigator-assigned outcome of failure, and those with an outcome of clinical cure who underwent a second procedure, were reviewed by an independent blinded surgical review panel comprising 3 surgeons and 2 radiologists. Source control was considered adequate when the physical and mechanical measures were consistent with current local standards of practice to eliminate the source of infection, control ongoing contamination, and restore gastrointestinal function [24]. Patients who were considered to have had inadequate source control were excluded from the per-protocol analyses.

Statistical Analysis

Prior to completion of the studies, statistical analyses were planned based on pooled data from the 2 trials. The planned pooled sample size ensured a minimum of 90% power to demonstrate the noninferiority of ceftolozane/tazobactam plus metronidazole to meropenem at a 10% noninferiority margin at a 1-sided significance level of 0.025. These calculations also assumed that 80% of randomized patients would meet the criteria to be included in the MITT population and that the clinical cure rate in both arms would be 75%.

The noninferiority hypothesis was tested through a 2-sided 95% confidence interval (CI) approach. The weighted difference in cure rates and the 95% CI around the difference in cure rates between study treatments were calculated using a stratified Newcombe CI with minimum risk weights [25, 26]. If the lower bound of the 95% CI for the difference (ceftolozane/tazobactam plus metronidazole minus meropenem) was above −10 percentage points, noninferiority was claimed.

Other secondary endpoints of clinical cure in the ITT and CE populations, various ME population subgroups, and per-baseline pathogen in the ME population were analyzed using a 95% CI calculated by the Wilson score methodology. Safety and tolerability of ceftolozane/tazobactam plus metronidazole were also evaluated. Statistical analyses were performed using SAS version 9.1.3 or higher (SAS Institute, Cary, North Carolina).

RESULTS

Patient Disposition and Baseline Characteristics

In total, 993 patients were randomized to ceftolozane/tazobactam plus metronidazole (n = 487) or meropenem (n = 506), and 806 (81.2%) qualified for the MITT population (Figure 1). Approximately 50% of patients in each treatment group received therapy for up to 7 days, and an additional 36.5% received
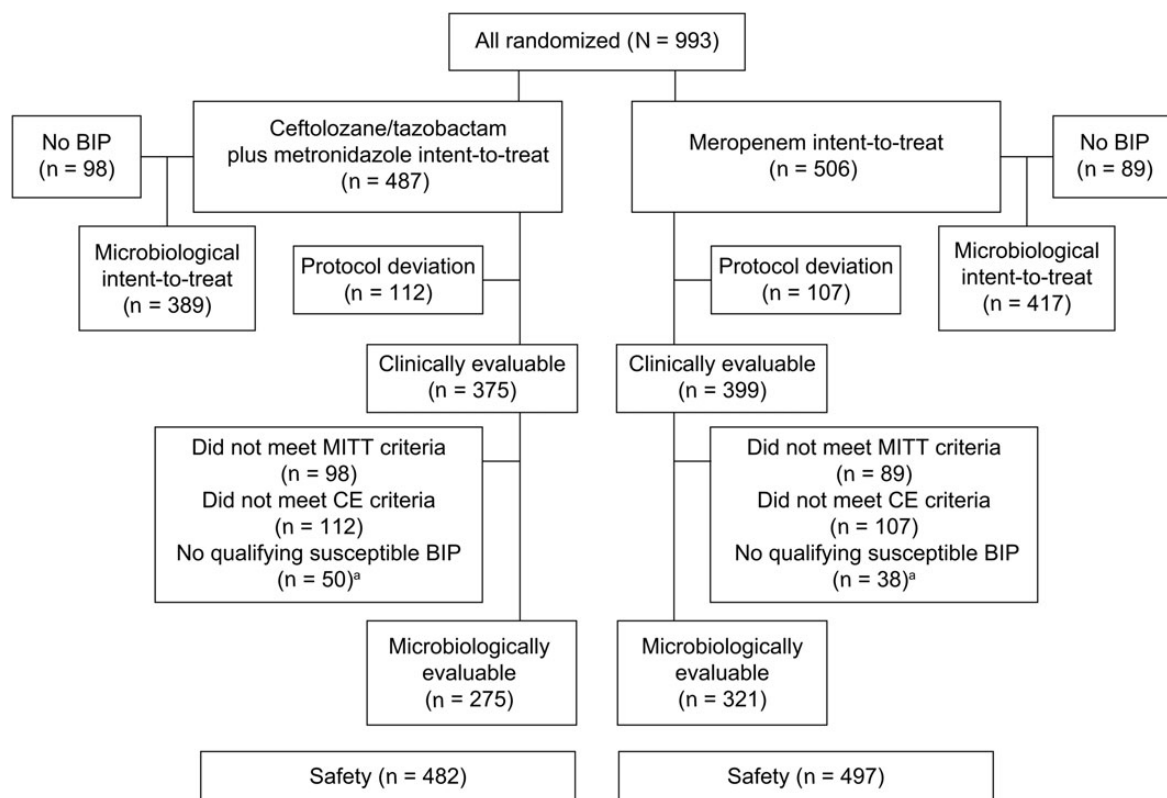
Figure 1. Patient disposition in ASPECT-cIAI (Assessment of the Safety Profile and Efficacy of Ceftolozane/Tazobactam in Complicated Intra-abdominal Infections). [a]Patients could be excluded for more than one reason. Abbreviations: BIP, baseline infecting pathogen; CE, clinically evaluable; MITT, microbiological ITT.

treatment for up to 10 days. The mean duration of treatment for patients who were eligible to continue therapy beyond 10 days is shown in Table 1.

The majority of participants were from Europe (76.9%), followed by South America (10.5%), North America (7.6%), and other geographic regions (5.0%). A list of participating investigators and their sites is provided in the Supplementary Data. Baseline demographic characteristics were similar between

Table 1. Duration of Therapy for Patients Who Were Eligible for Extension of Treatment Beyond 10 Days (Microbiological Intent-to-Treat Population)

Diagnosis	Mean Duration of Therapy, d	Min–Max, d
Multiple abscess (n = 64)	9.6	2–15
Diffuse peritonitis, nonappendix (n = 149)	8.6	2–15
Failed prior therapy, nonappendix (n = 42)	9.3	2–15
Localized complicated appendicitis (n = 254)[a]	7.0	2–15

[a] Patients were not eligible for extension of treatment beyond 10 days.

treatment groups (Table 2). The most common origin of infection was the appendix, and the most common diagnosis was appendiceal perforation or abscess (Table 3).

Pathogens at Baseline

The incidence and distribution of baseline pathogens were similar between the treatment groups. The most common gram-negative aerobes isolated at baseline from intra-abdominal specimens in the MITT population were *Escherichia coli* (525/806 [65.1%]), *Klebsiella pneumoniae* (76/806 [9.4%]), and *P. aeruginosa* (72/806 [8.9%]). The majority of infections were polymicrobial (257/389 [66.1%] and 288/417 [69.1%] patients in the ceftolozane/tazobactam plus metronidazole and meropenem treatment groups, respectively). There were 29 ESBL-producing Enterobacteriaceae isolated in each treatment group, an overall rate of 7.2% (58/806). Of 52 individual *P. aeruginosa* isolates for which MIC data were available, 3 (5.8%) isolates were resistant to ≥3 drug classes known to be active against *P. aeruginosa*, and 6 (11.5%) were nonsusceptible to ≥3 antipseudomonal drug classes.

The MIC required to inhibit the growth of 90% (MIC_{90}) of Enterobacteriaceae was 1 mg/L for ceftolozane/tazobactam and 0.063 mg/L for meropenem. For *P. aeruginosa*, the MIC_{90}

Table 2. Baseline Demographics (Microbiological Intent-to-Treat Population)

Characteristic	Ceftolozane/Tazobactam Plus Metronidazole (n = 389)	Meropenem (n = 417)
Sex, male, No. (%)	218 (56.0)	248 (59.5)
Race, white, No. (%)	367 (94.3)	388 (93.0)
Age, y		
Mean (SD)	50.8 (18.3)	50.4 (16.9)
18–64, No. (%)	289 (74.3)	332 (79.6)
65–74, No. (%)	54 (13.9)	48 (11.5)
≥75, No. (%)	46 (11.8)	37 (8.9)
Body mass index, kg/m^2, mean (SD)	26.76 (5.5)	27.07 (5.3)
Baseline APACHE II score, No. (%)[a]		
Mean (SD)	6.2 (4.2)	6.0 (4.1)
0–5	191 (49.2)	213 (51.1)
6–10	143 (36.9)	153 (36.7)
11–15	42 (10.8)	38 (9.1)
>15	12 (3.1)	13 (3.1)
Presence of bacteremia	8 (2.1)	12 (2.9)
Creatinine clearance, No. (%)		
Mild renal impairment (50 to 79 mL/min)	98 (25.2)	109 (26.1)
Moderate renal impairment (30–49 mL/min)	23 (5.9)	13 (3.1)
Severe renal impairment (<30 mL/min)	0	0

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; SD, standard deviation.

[a] Data missing in 1 patient.

values for each study drug were 1 mg/L and 2 mg/L, respectively. Susceptibility rates to ceftolozane/tazobactam and meropenem were 97.4% and 99.9% for Enterobacteriaceae and 98.6% and 89.9% for *P. aeruginosa*, respectively.

Source Control Review Panel Findings

The surgical review panel reviewed 73 patients. Twenty-four patients (12 in each treatment group) were considered to have had inadequate source control and were excluded from the CE and ME populations. Of the 9 patients who were considered to have obtained clinical cure by the investigator but required a second procedure, the surgical review panel changed 2 patients' outcomes (1 per treatment arm) from cure to failure because of evidence of ongoing infection at the time of the second intervention.

Efficacy Analysis

For the primary endpoint, clinical cure rates were 83.0% (323/389) with ceftolozane/tazobactam plus metronidazole and 87.3% (364/417) with meropenem in the MITT population at

Table 3. Site of Infections, Diagnoses, Disease Characteristics, and Source Control Procedures (Microbiological Intent-to-Treat Population)

Characteristic	Ceftolozane/Tazobactam Plus Metronidazole (n = 389)	Meropenem (n = 417)
Origin of current infection, No. (%)[a]		
Appendix	179 (46.0)	205 (49.2)
Biliary–cholecystitis	73 (18.8)	69 (16.5)
Colon	56 (14.4)	62 (14.9)
Stomach/duodenum	40 (10.3)	39 (9.4)
Small bowel	23 (5.9)	19 (4.6)
Parenchymal (liver)	16 (4.1)	17 (4.1)
Parenchymal (spleen)	2 (0.5)	2 (0.5)
Biliary–cholangitis	1 (0.3)	0
Diagnosis, No. (%)[b]		
Appendiceal perforation or abscess	175 (45.0)	203 (48.7)
Cholecystitis with rupture, perforation, or progression of infection	72 (18.5)	69 (16.5)
Peritonitis due to other perforated viscus or following a prior operative procedure	41 (10.5)	33 (7.9)
Acute gastric or duodenal perforation	38 (9.8)	33 (7.9)
Diverticular disease with perforation or abscess	29 (7.5)	36 (8.6)
Other IAI abscess (including liver and spleen)	29 (7.5)	36 (8.6)
Traumatic intestinal perforation	5 (1.3)	7 (1.7)
Abscess present, No. (%)	219 (56.3)	240 (57.6)
Multiple abscesses[c]	33 (15.1)	32 (13.3)
Peritonitis present, No. (%)	337 (86.6)	340 (81.5)
Local[d]	198 (58.8)	203 (59.7)
Diffuse[d]	139 (41.2)	137 (40.3)
Localized complicated appendicitis, No. (%)	115 (29.6)	142 (34.1)
Etiological mechanism, No. (%)		
Postoperative infection	27 (6.9)	28 (6.7)
Trauma	4 (1.0)	8 (1.9)
Spontaneous rupture	277 (71.2)	302 (72.4)
Malignancy	11 (2.8)	13 (3.1)
Other	70 (18.0)	66 (15.8)
Procedure type, No. (%)[e]		
Laparotomy	274 (70.4)	272 (65.2)
Laparoscopy	86 (22.1)	105 (25.2)
Percutaneous aspiration	24 (6.2)	37 (8.9)
Other[f]	5 (1.3)	4 (1.0)

Percentages are calculated as 100 × (no./No.), except where indicated by a footnote.

Abbreviation: IAI, intra-abdominal infection.

[a] Investigator could choose >1 site; totals are not mutually exclusive.

[b] Investigator could chose only 1 diagnosis.

[c] Percentages are calculated 100 × (no./No. of patients with abscess present).

[d] Percentages are calculated 100 × (no./No. of patients with peritonitis present).

[e] Patients could have multiple procedure types.

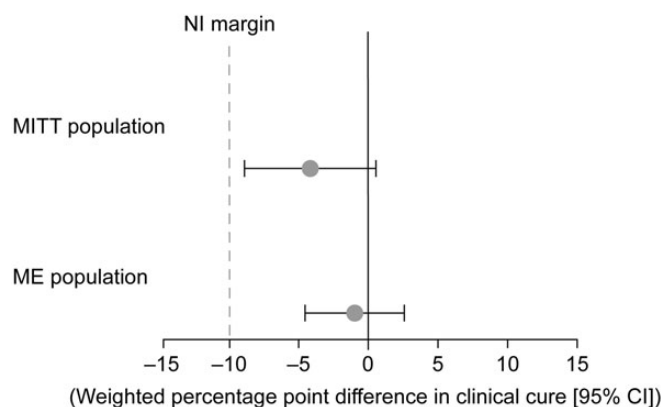[f] Other procedures included appendectomy and esophagogastroduodenoscopy.

	Ceftolozane/ tazobactam plus metronidazole No. (%)	Meropenem No. (%)	Percentage difference (95% CI)
MITT population	n = 389	n = 417	
Cure	323 (83.0)	364 (87.3)	−4.2 (−8.91 to .54)
Failure	32 (8.2)	34 (8.2)	
Indeterminate	34 (8.7)	19 (4.6)	
ME population	n = 275	n = 321	
Cure	259 (94.2)	304 (94.7)	−1.0 (−4.52 to 2.59)
Failure	16 (5.8)	17 (5.3)	

Figure 2. Primary and secondary analysis endpoints at the test-of-cure visit. In the microbiological intent-to-treat (MITT) population, a treatment failure approach was used, where indeterminate clinical responses were imputed as failures. In the microbiologically evaluable (ME) population, a data-as-observed approach was used, where indeterminate clinical responses were excluded from the analysis. Abbreviations: CI, confidence interval; NI, non-inferiority margin.

the TOC visit, which occurred at a median of 27 days (interquartile range, 26–28 days) after the TOC visit. The weighted difference in clinical cure rates (ceftolozane/tazobactam plus metronidazole minus meropenem) was −4.2% with a 2-sided 95% CI of −8.91% to .54%, thus meeting the statistical criteria for noninferiority. Statistical noninferiority was also demonstrated for the ME population, where clinical cure rates were 94.2% and 94.7% (weighted difference, −1.0; 95% CI, −4.52 to 2.59) at the TOC visit (Figure 2). Clinical cure rates in the ITT population at TOC were 83.6% for ceftolozane/tazobactam plus metronidazole and 86.2% for meropenem (difference, −2.6; 95% CI, −7.08 to 1.87), similar to those observed in the MITT population. In the CE population, cure rates were 94.1% and 94.0%, respectively (difference, 0.1; 95% CI, −3.30 to 3.55). At the end of therapy, clinical cure rates in the MITT population were higher in both treatment groups: 89.2% for ceftolozane/tazobactam plus metronidazole and 92.3% for meropenem (difference, −3.1; 95% CI, −7.23 to .89).

In both treatment groups, 8.2% of patients in the MITT populations failed treatment at the TOC visit (Figure 2). The most common reasons for failure were persisting or recurrent abdominal infection requiring an additional intervention (2.8% of failures in the ceftolozane/tazobactam plus metronidazole group and 3.6% in the meropenem group) and the requirement for additional antibiotics for ongoing cIAI (3.3% and 2.6%, respectively, for each treatment group). Other reasons for failure were postsurgical wound infection and death due to cIAI.

Clinical outcomes in the subgroup analyses were generally consistent with the primary and secondary analyses, with no meaningful differences recorded between treatments. Clinical cure rates with both treatments were generally lower in high-

risk patients (elderly patients and those with higher APACHE II scores, moderate renal impairment, or small bowel and colon infections) vs the overall ME population (Table 4).

Per-pathogen clinical cure rates were similar between groups (Supplementary Table 2). In all patients with ESBL-producing Enterobacteriaceae, the clinical cure rate was 95.8% (23/24) in the ceftolozane/tazobactam plus metronidazole group and 88.5% (23/26) in the meropenem group (Supplementary Figure). In patients with CTX-M-14/15 ESBL-producing Enterobacteriaceae, clinical cure was observed in 13 of 13 (100%) and 8 of 11 (72.7%) patients, respectively.

Safety

The incidence of AEs that developed during treatment was similar between the ceftolozane/tazobactam plus metronidazole group and the meropenem group (44.0% and 42.7%, respectively), and most events were mild to moderate in severity. The AEs occurring in ≥2% of patients in either treatment group are shown in Table 5. The most common laboratory AEs were increased alanine aminotransferase and aspartate aminotransferase, which occurred in 2.5% and 1.6% of all patients, respectively. Drug-related AEs leading to discontinuation were few, occurring in 3 patients (0.6%) in the ceftolozane/tazobactam plus metronidazole group and 4 patients (0.8%) in the meropenem group.

Serious AEs occurred in 39 of 482 (8.1%) and 36 of 497 (7.2%) patients in the ceftolozane/tazobactam plus metronidazole and meropenem groups, respectively. Drug-related serious AEs occurred in 1 patient in each treatment group (both *Clostridium difficile* infection).

There were 11 deaths (2.3%) in the ceftolozane/tazobactam plus metronidazole group and 8 deaths (1.6%) in the meropenem

Table 4. Subgroup Analysis of Clinical Cure at the Test-of-Cure Visit (Microbiologically Evaluable Population)

Clinical Cure no./No. (%)	Ceftolozane/Tazobactam Plus Metronidazole (n = 275)	Meropenem (n = 321)	Percentage Difference (95% CI)
Sex			
Male	147/157 (93.6)	182/189 (96.3)	−2.7 (−7.97 to 2.05)
Female	112/118 (94.9)	122/132 (92.4)	2.5 (−4.04 to 8.91)
Age, y			
18–64	206/214 (96.3)	249/262 (95.0)	1.2 (−2.80 to 5.03)
65–74	30/35 (85.7)	36/38 (94.7)	−9.0 (−24.59 to 5.43)
≥75	23/26 (88.5)	19/21 (90.5)	−2.0 (−20.76 to 18.79)
Region			
Eastern Europe	213/221 (96.4)	239/247 (96.8)	−0.4 (−4.10 to 3.12)
Western Europe	2/5 (40.0)	7/11 (63.6)	−23.6 (−58.95 to 22.86)
North America	8/11 (72.7)	10/11 (90.9)	−18.2 (−48.41 to 15.40)
South America	28/28 (100)	40/42 (95.2)	4.8 (−7.78 to 15.79)
Rest of world	8/10 (80.0)	8/10 (80.0)	0 (−34.14 to 34.14)
APACHE II score			
<10	213/222 (95.9)	262/274 (95.6)	0.3 (−3.61 to 3.98)
≥10	45/52 (86.5)	42/47 (89.4)	−2.8 (−16.08 to 10.92)
Baseline CrCl, mL/min			
<50	8/11 (72.7)	5/7 (71.4)	1.3 (−34.37 to 40.92)
≥50	251/264 (95.1)	299/314 (95.2)	−0.1 (−3.95 to 3.43)
Prior antibiotic use			
Yes	133/145 (91.7)	163/177 (92.1)	−0.4 (−6.81 to 5.69)
No	126/130 (96.9)	141/144 (97.9)	−1.0 (−5.76 to 3.30)
Primary site of infection			
Bowel (small or large)	35/43 (81.4)	51/57 (89.5)	−8.1 (−23.17 to 5.74)
Other site of IAI	224/232 (96.6)	253/264 (95.8)	0.7 (−2.97 to 4.28)
Anatomic site of infection			
Appendix	136/141 (96.5)	172/179 (96.1)	0.4 (−4.55 to 4.79)
Nonappendix	123/134 (91.8)	132/142 (93.0)	−1.2 (−7.86 to 5.33)
Biliary–cholangitis	1/1 (100)	0/0	NC
Biliary–cholecystitis	49/50 (98.0)	43/46 (93.5)	4.5 (−4.99 to 15.63)
Colon	25/31 (80.6)	39/42 (92.9)	−12.2 (−29.77 to 3.41)
Parenchymal (liver)	9/10 (90.0)	8/8 (100)	−10.0 (−40.42 to 23.46)
Parenchymal (spleen)	2/2 (100)	1/1 (100)	0 (−65.76 to 79.35)
Small bowel	11/13 (84.6)	12/15 (80.0)	4.6 (−25.20 to 32.12)
Stomach/duodenum	28/30 (93.3)	26/26 (100)	−6.7 (−21.32 to 7.08)
Other	5/5 (100)	5/6 (83.3)	16.7 (−28.88 to 56.35)
Peritonitis type			
Localized	126/132 (95.5)	152/161 (94.4)	1.0 (−4.62 to 6.34)
Diffuse	98/104 (94.2)	108/114 (94.7)	−0.5 (−7.37 to 6.02)
No. of abscesses			
Single	116/124 (93.5)	146/152 (96.1)	−2.5 (−8.65 to 2.90)
Multiple	22/25 (88.0)	23/25 (92.0)	−4.0 (−22.86 to 14.69)
Procedure type			
Percutaneous aspiration	14/14 (100)	23/23 (100)	0 (−21.53 to 14.31)
Laparoscopy	63/66 (95.5)	73/81 (90.1)	5.3 (−3.98 to 14.27)
Laparotomy	181/193 (93.8)	207/217 (95.4)	−1.6 (−6.42 to 2.90)

Regions are defined as follows: Eastern Europe (Bulgaria, Croatia, Estonia, Georgia, Hungary, Latvia, Lithuania, Poland, Republic of Moldova, Romania, Russia, Serbia, Slovakia, Ukraine); Western Europe (Belgium, Germany, Spain); North America (Mexico, United States); South America (Argentina, Brazil, Chile, Colombia, Peru); and rest of world (Australia, Israel, South Africa, South Korea).

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; CI, confidence interval; CrCl, creatinine clearance; IAI, intra-abdominal infection; NC, not calculated.

Table 5. Adverse Events Occurring in ≥2% of Patients in Either Treatment Group (Safety Population)

Adverse Event No. (%)	Ceftolozane/Tazobactam Plus Metronidazole (n = 482)	Meropenem (n = 497)
Any adverse event	212 (44.0)	212 (42.7)
Nausea	38 (7.9)	29 (5.8)
Diarrhea	30 (6.2)	25 (5.0)
Vomiting	16 (3.3)	20 (4.0)
Pyrexia	25 (5.2)	20 (4.0)
Hypokalemia	14 (2.9)	8 (1.6)
Insomnia	17 (3.5)	11 (2.2)
Headache	12 (2.5)	9 (1.8)
Anemia, postoperative	10 (2.1)	8 (1.6)
Hypertension	9 (1.9)	10 (2.0)

group; no death was considered by the investigators to be related to study treatment.

DISCUSSION

The increasing prevalence of multidrug-resistant, gram-negative organisms in serious infections is an important concern, and has led to the development of new therapeutic agents [19, 27, 28]. In this trial, the efficacy and safety of the novel antimicrobial agent ceftolozane/tazobactam were evaluated in patients with mostly community-acquired cIAIs. One-fifth of patients were aged ≥65 years, one-third had renal impairment, >80% had peritonitis, and the most frequent site of infection was the appendix. These factors attest to the high degree of illness severity in the patients who were enrolled in this trial. Although the microbiology of infecting pathogens was similar to that observed in other phase 3 studies in this indication [29–32], the overall rate of infection with ESBL-positive isolates (7.2%) was higher than in previous observations [29, 30]. The key finding from this study was that intravenous ceftolozane/tazobactam (1.5 g) plus metronidazole (500 mg) every 8 hours was noninferior to the comparator treatment, intravenous meropenem (1 g) every 8 hours, when administered for 4–14 days for the treatment of cIAIs.

Ceftolozane/tazobactam plus metronidazole demonstrated high clinical cure rates in patients infected with the common cIAI pathogens including *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *Enterobacter cloacae*, and *Klebsiella oxytoca*, as well as *Streptococcus anginosus*, *Streptococcus constellatus*, and *Streptococcus salivarius*.

As with other cephalosporins [31, 33–35], the AEs reported most frequently were gastrointestinal symptoms of nausea, vomiting, and diarrhea and are expected events in a postoperative population with cIAI.

Activity Against Extended-Spectrum β-Lactamases
In the past 10 years, ESBL-producing Enterobacteriaceae have become an important challenge for antibiotic treatment of infections,

and ESBL carriage rates are increasing in nearly all geographic areas [36]. In the United States, up to 19% of healthcare-associated infections are due to ESBL-producing Enterobacteriaceae, constituting a serious threat of resistance [37]. For severe ESBL infections, carbapenems have become the drugs of choice [38].

Ceftolozane/tazobactam showed substantial clinical and microbiological activity against ESBL-producing *E. coli* and *Klebsiella* strains. The ESBL-positive rate is consistent with observations from the Study for Monitoring Antimicrobial Resistance Trends, a global surveillance program of gram-negative bacilli from IAIs. This European study characterized >3000 patient isolates in 2008, revealing ESBL rates of 11.6% in *E. coli* and 17.9% in *K. pneumoniae* [39].

CTX-M–type ESBLs are by far the most common ESBLs worldwide, and are often associated with multidrug resistance in Enterobacteriaceae [11, 36]. In our study, more than one-half of the ESBL-producing Enterobacteriaceae isolated at baseline were positive for CTX-M-14 or CTX-M-15–type enzymes, but no *K. pneumoniae* carbapenemase enzymes were identified. Ceftolozane/tazobactam plus metronidazole maintained clinical efficacy against these highly resistant strains (100%) compared with 72.7% with meropenem.

Activity Against *Pseudomonas aeruginosa*
Multidrug-resistant *P. aeruginosa* often requires complex antimicrobial regimens and, when treated inadequately, infections caused by this pathogen are associated with particularly poor outcomes including postoperative complications, longer hospital stays, and increased mortality [5, 6, 40–42]. In vitro studies have shown that ceftolozane/tazobactam is the most potent antipseudomonal agent, maintaining activity against many multidrug-resistant strains [13]. Ceftolozane/tazobactam demonstrated efficacy against *P. aeruginosa*, even though experience with multidrug-resistant *P. aeruginosa* was limited.

In conclusion, these results suggest that ceftolozane/tazobactam plus metronidazole is a potential alternative to the currently recommended antimicrobials for the treatment of cIAIs, especially when resistant Enterobacteriaceae or *P. aeruginosa* are suspected, such as in healthcare-associated infections.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

References

1. Herzog T, Chromik AM, Uhl W. Treatment of complicated intra-abdominal infections in the era of multi-drug resistant bacteria. Eur J Med Res 2010; 15:525–32.
2. Barie PS, Hydo LJ, Eachempati SR. Longitudinal outcomes of intra-abdominal infection complicated by critical illness. Surg Infect (Larchmt) 2004; 5:365–73.
3. Gauzit R, Péan Y, Barth X, Mistretta F, Lalaude O. Epidemiology, management, and prognosis of secondary non-postoperative peritonitis: a French prospective observational multicenter study. Surg Infect (Larchmt) 2009; 10:119–27.
4. Sartelli M, Catena F, Ansaloni L, et al. Complicated intra-abdominal infections worldwide: the definitive data of the CIAOW Study. World J Emerg Surg 2014; 9:37.
5. Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis 2010; 50:133–64.
6. Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Surg Infect (Larchmt) 2010; 11:79–109.
7. Edelsberg J, Berger A, Schell S, Mallick R, Kuznik A, Oster G. Economic consequences of failure of initial antibiotic therapy in hospitalized adults with complicated intra-abdominal infections. Surg Infect (Larchmt) 2008; 9:335–47.
8. Sturkenboom MC, Goettsch WG, Picelli G, et al. Inappropriate initial treatment of secondary intra-abdominal infections leads to increased risk of clinical failure and costs. Br J Clin Pharmacol 2005; 60:438–43.
9. Bare M, Castells X, Garcia A, Riu M, Comas M, Egea MJ. Importance of appropriateness of empiric antibiotic therapy on clinical outcomes in intra-abdominal infections. Int J Technol Assess Health Care 2006; 22:242–8.
10. Kumar A, Ellis P, Arabi Y, et al. Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock. Chest 2009; 136:1237–48.
11. Bush K. Proliferation and significance of clinically relevant beta-lactamases. Ann N Y Acad Sci 2013; 1277:84–90.
12. Morrissey I, Hackel M, Badal R, Bouchillon S, Hawser S, Biedenbach D. A review of ten years of the Study for Monitoring Antimicrobial Resistance Trends (SMART) from 2002 to 2011. Pharmaceuticals (Basel) 2013; 6:1335–46.
13. Farrell DJ, Flamm RK, Sader HS, Jones RN. Antimicrobial activity of ceftolozane-tazobactam tested against Enterobacteriaceae and *Pseudomonas aeruginosa* with various resistance patterns isolated in U.S. hospitals (2011–2012). Antimicrob Agents Chemother 2013; 57:6305–10.
14. Sader HS, Farrell DJ, Flamm RK, Jones RN. Ceftolozane/tazobactam activity tested against aerobic gram-negative organisms isolated from intra-abdominal and urinary tract infections in European and United States hospitals (2012). J Infect 2014; 69:266–77.
15. Sader HS, Farrell DJ, Castanheira M, Flamm RK, Jones RN. Antimicrobial activity of ceftolozane/tazobactam tested against *Pseudomonas aeruginosa* and Enterobacteriaceae with various resistance patterns isolated in European hospitals (2011–12). J Antimicrob Chemother 2014; 69:2913–722.
16. Walkty A, Karlowsky JA, Adam H, et al. In vitro activity of ceftolozane-tazobactam against *Pseudomonas aeruginosa* isolates obtained from patients in Canadian hospitals in the CANWARD study, 2007 to 2012. Antimicrob Agents Chemother 2013; 57:5707–9.
17. Brown NP, Pillar CM, Draghi DC, et al. Activity profile of CXA-101 against gram-positive and gram-negative pathogens by broth and agar dilution. In: 48th Annual International Conference on Antimicrobial Agents and Chemotherapy, Washington, DC, 25–28 October 2008. Poster F1-354.
18. Lucasti C, Hershberger E, Miller B, et al. A multicenter, double-blind, randomized, phase II trial to assess the safety and efficacy of ceftolozane/tazobactam plus metronidazole compared with meropenem in adult patients with complicated intra-abdominal infections. Antimicrob Agents Chemother 2014; 58:5350–7.
19. US Food and Drug Administration. Guidance for industry. Antibacterial therapies for patients with unmet medical need for the treatment of serious bacterial diseases. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM359184.pdf. Accessed 15 June 2014.
20. Miller B, Hershberger E, Benziger D, Trinh M, Friedland I. Pharmacokinetics and safety of intravenous ceftolozane-tazobactam in healthy adult subjects following single and multiple ascending doses. Antimicrob Agents Chemother 2012; 56:3086–91.
21. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013; 41:580–637.
22. Centers for Disease Control and Prevention. Surveillance definitions for specific types of infections. Available at: http://www.cdc.gov/nhsn/PDFs/pscManual/17pscNosInfDef_current.pdf. Accessed 19 February 2015.
23. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing; 22nd informational supplement. Wayne, PA: CLSI, 2012.
24. Schein M, Marshall J. Source control for surgical infections. World J Surg 2004; 28:638–45.
25. Yan X, Su XG. Stratified Wilson and Newcombe confidence intervals for multiple binomial proportions. Stat Biopharm Res 2010; 2:329–35.
26. Mehrotra DV, Railkar R. Minimum risk weights for comparing treatments in stratified binomial trials. Stat Med 2000; 19:811–25.
27. Boucher HW, Talbot GH, Benjamin DK Jr, et al. 10×'20 progress—development of new drugs active against gram-negative bacilli: an update from the Infectious Diseases Society of America. Clin Infect Dis 2013; 56:1685–94.
28. World Health Organization. Antimicrobial resistance. Global report on surveillance. Available at: http://www.who.int/drugresistance/documents/surveillancereport/en/. Accessed 19 September 2014.
29. De Waele JJ, Tellado JM, Alder J, et al. Randomised clinical trial of moxifloxacin versus ertapenem in complicated intra-abdominal infections: results of the PROMISE study. Int J Antimicrob Agents 2013; 41:57–64.
30. Oliva ME, Rekha A, Yellin A, et al. A multicenter trial of the efficacy and safety of tigecycline versus imipenem/cilastatin in patients with complicated intra-abdominal infections [Study ID numbers: 3074A1–301-WW; ClinicalTrials.gov identifier: NCT00081744]. BMC Infect Dis 2005; 5:88.
31. Qvist N, Warren B, Leister-Tebbe H, et al. Efficacy of tigecycline versus ceftriaxone plus metronidazole for the treatment of complicated intra-abdominal infections: results from a randomized, controlled trial. Surg Infect (Larchmt) 2012; 13:102–9.

32. Solomkin JS, Yellin AE, Rotstein OD, et al. Ertapenem versus piperacillin/tazobactam in the treatment of complicated intraabdominal infections: results of a double-blind, randomized comparative phase III trial. Ann Surg **2003**; 237:235–45.

33. Lucasti C, Popescu I, Ramesh MK, Lipka J, Sable C. Comparative study of the efficacy and safety of ceftazidime/avibactam plus metronidazole versus meropenem in the treatment of complicated intra-abdominal infections in hospitalized adults: results of a randomized, double-blind, phase II trial. J Antimicrob Chemother **2013**; 68:1183–92.

34. Low DE, File TM Jr, Eckburg PB, et al. FOCUS 2: a randomized, double-blinded, multicentre, phase III trial of the efficacy and safety of ceftaroline fosamil versus ceftriaxone in community-acquired pneumonia. J Antimicrob Chemother **2011**; 66(Suppl 3):iii33–44.

35. File TM Jr, Low DE, Eckburg PB, et al. FOCUS 1: a randomized, double-blinded, multicentre, phase III trial of the efficacy and safety of ceftaroline fosamil versus ceftriaxone in community-acquired pneumonia. J Antimicrob Chemother **2011**; 66(Suppl 3):iii19–32.

36. Woerther PL, Burdet C, Chachaty E, Andremont A. Trends in human fecal carriage of extended-spectrum beta-lactamases in the community: toward the globalization of CTX-M. Clin Microbiol Rev **2013**; 26: 744–58.

37. Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States, **2013**. Available at: http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf. Accessed 12 June 2014.

38. Vardakas KZ, Tansarli GS, Rafailidis PI, Falagas ME. Carbapenems versus alternative antibiotics for the treatment of bacteraemia due to Enterobacteriaceae producing extended-spectrum beta-lactamases: a systematic review and meta-analysis. J Antimicrob Chemother **2012**; 67:2793–803.

39. Hawser S, Hoban D, Bouchillon S, Badal R, Carmeli Y, Hawkey P. Antimicrobial susceptibility of intra-abdominal gram-negative bacilli from Europe: SMART Europe 2008. Eur J Clin Microbiol Infect Dis **2011**; 30:173–9.

40. Augustin P, Dinh AT, Valin N, et al. *Pseudomonas aeruginosa* postoperative peritonitis: clinical features, risk factors, and prognosis. Surg Infect (Larchmt) **2013**; 14:297–303.

41. Hoban DJ, Bouchillon SK, Hawser SP, Badal RE, Labombardi VJ, DiPersio J. Susceptibility of gram-negative pathogens isolated from patients with complicated intra-abdominal infections in the United States, 2007–2008: results of the Study for Monitoring Antimicrobial Resistance Trends (SMART). Antimicrob Agents Chemother **2010**; 54:3031–4.

42. Micek ST, Lloyd AE, Ritchie DJ, Reichley RM, Fraser VJ, Kollef MH. *Pseudomonas aeruginosa* bloodstream infection: importance of appropriate initial antimicrobial treatment. Antimicrob Agents Chemother **2005**; 49:1306–11.