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SUSCEPTIBILITY

In Vitro Activity of Ceftazidime-Avibactam against Isolates from Patients in a Phase 3 Clinical Trial for Treatment of Complicated Intra-abdominal Infections

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ABSTRACT The increasing prevalence of multidrug-resistant Gram-negative pathogens has generated a requirement for new treatment options. Avibactam, a novel non-β-lactam–β-lactamase inhibitor, restores the activity of ceftazidime against Ambler class A, C, and some class D β-lactamase-producing strains of *Enterobacteriaceae* and *Pseudomonas aeruginosa*. The *in vitro* activities of ceftazidime-avibactam versus comparators were evaluated against 1,440 clinical isolates obtained in a phase 3 clinical trial in patients with complicated intra-abdominal infections (cIAI; ClinicalTrials.gov identifier NCT01499290). Overall, *in vitro* activities were determined for 803 *Enterobacteriaceae*, 70 *P. aeruginosa*, 304 Gram-positive aerobic, and 255 anaerobic isolates obtained from 1,066 randomized patients at baseline. Susceptibility was determined by broth microdilution. The most commonly isolated Gram-negative, Gram-positive, and anaerobic pathogens were *Escherichia coli* ($n = 549$), *Streptococcus anginosus* ($n = 130$), and *Bacteroides fragilis* ($n = 96$), respectively. Ceftazidime-avibactam was highly active against isolates of *Enterobacteriaceae*, with an overall MIC_{90} of 0.25 mg/liter. In contrast, the MIC_{90} for ceftazidime alone was 32 mg/liter. The MIC_{90} value for ceftazidime-avibactam (4 mg/liter) was one dilution lower than that of ceftazidime alone (8 mg/liter) against isolates of *Pseudomonas aeruginosa*. The ceftazidime-avibactam MIC_{90} for 109 ceftazidime-nonsusceptible *Enterobacteriaceae* isolates was 2 mg/liter, and the MIC range for 6 ceftazidime-nonsusceptible *P. aeruginosa* isolates was 8 to 32 mg/liter. The MIC_{90} values were within the range of susceptibility for the study drugs permitted per the protocol in the phase 3 study to provide coverage for aerobic Gram-positive and anaerobic pathogens. These findings demonstrate the *in vitro* activity of ceftazidime-avibactam against bacterial pathogens commonly observed in cIAI patients, including ceftazidime-nonsusceptible *Enterobacteriaceae*. (This study has been registered at ClinicalTrials.gov under identifier NCT01499290.)

KEYWORDS ceftazidime-avibactam, complicated intra-abdominal infection, *in vitro* activity, ceftazidime-nonsusceptible

The increasing prevalence of β-lactamase-mediated antibiotic resistance has generated a need for the development of new treatment options (1). Avibactam is a novel non-β-lactam–β-lactamase inhibitor with *in vitro* activity against Ambler class A and C β-lactamases (including *Klebsiella pneumoniae* carbapenemase [KPC] and the carbapenem-hydrolyzing oxacillinase OXA-48), as well as some class D enzymes (2, 3). Ceftazidime is an established antipseudomonal cephalosporin; since its introduction, a number of new extended-spectrum β-lactamases have been identified, eroding the effectiveness of ceftazidime and other cephalosporins (1). When combined with avibactam, the *in vitro* spectrum of activity of ceftazidime is extended to include isolates

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producing extended-spectrum β-lactamases (ESBLs) and AmpC-producing *Enterobacteriaceae* and *Pseudomonas aeruginosa* (4–7).

Ceftazidime-avibactam has been approved in Europe, the United States, and several other countries for the treatment of adults with complicated intra-abdominal infection (cIAI) in combination with metronidazole and complicated urinary tract infection (cUTI) (8, 9). In addition, in Europe, ceftazidime-avibactam has been approved for the treatment of hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP) and other aerobic Gram-negative infections for which there are limited treatment options (8).

Ceftazidime-avibactam has been investigated in two identical prospective randomized double-blind comparative phase 3 noninferiority studies in patients with cIAI (RECLAIM; ClinicalTrials.gov identifier NCT01499290) (10). These were combined and analyzed as one study and demonstrated the efficacy, safety, and tolerability of ceftazidime-avibactam plus metronidazole in comparison with meropenem in patients with cIAI. As part of this study, bacterial cultures were isolated from abdominal and blood specimens in patients with confirmed cIAI and submitted to a central reference laboratory for identification and susceptibility testing. This report describes the *in vitro* activities of ceftazidime-avibactam and relevant comparator agents against these clinical isolates.

RESULTS

In total, 1,440 isolates from 1,066 randomized patients in the phase 3 cIAI clinical trial RECLAIM (ClinicalTrials.gov identifier NCT01499290) were sent to the central laboratory for identification and susceptibility testing. Of these isolates, 803 isolates were *Enterobacteriaceae*, and 70 isolates were *P. aeruginosa*. *Escherichia coli* was the most common member of the *Enterobacteriaceae* to be identified (isolated in 549 of the randomized patients [51.5%]), followed by *K. pneumoniae* (100 patients [9.4%]). *Citrobacter freundii* complex and *Klebsiella oxytoca* were the third most commonly isolated *Enterobacteriaceae* (isolated in 32 patients each [3.0%]).

In total, 304 Gram-positive aerobes and 255 anaerobes were isolated at baseline. Of the Gram-positive aerobes, baseline isolates most frequently belonged to the *Streptococcus anginosus* group (130 isolates [12.2%]), followed by *Enterococcus faecalis* (59 isolates [5.5%]) and *Enterococcus faecium* (39 isolates [3.7%]). *Bacteroides fragilis* was the most frequently isolated anaerobe (96 isolates [9.0%]).

***In vitro* activity against Gram-negative isolates.** The *in vitro* activities of ceftazidime-avibactam, ceftazidime alone, and comparator agents against *Enterobacteriaceae* and *P. aeruginosa* are summarized in Table 1. The MIC_{50} and MIC_{90} values for ceftazidime alone against all *Enterobacteriaceae* isolates were 0.12 mg/liter and 32 mg/liter, respectively (Table 1). In contrast, ceftazidime-avibactam was highly active against *Enterobacteriaceae* isolates, with overall MIC_{50} and MIC_{90} values of 0.12 mg/liter and 0.25 mg/liter, respectively, confirming a 128-fold reduction in MIC_{90} for ceftazidime-avibactam compared with ceftazidime alone (Table 1).

With respect to the individual members of the *Enterobacteriaceae* family, the ceftazidime-avibactam MIC_{90} values for *E. coli* and *K. pneumoniae* (the most commonly isolated Gram-negative pathogens in this study) were 0.12 mg/liter and 0.5 mg/liter, respectively. In addition, the MIC_{90} values were ≤2 mg/liter for all the other members of the *Enterobacteriaceae* family where there were 10 or more isolates (Table 1). A group of nine other members of the *Enterobacteriaceae* family (where there were fewer individual isolates), including *Citrobacter farmeri* (1 isolate), *Citrobacter koseri* (5 isolates), *Hafnia alvei* (3 isolates), *Morganella morganii* (9 isolates), *Proteus vulgaris* group species (7 isolates), *Providencia rettgeri* (2 isolates), *Raoultella planticola* (2 isolates), *Salmonella* species (1 isolate), and *Serratia marcescens* (4 isolates) tested with a ceftazidime-avibactam MIC range of 0.015 to 1 mg/liter.

For the 70 *P. aeruginosa* isolates, the ceftazidime-avibactam MIC_{50} and MIC_{90} values were 2 mg/liter and 4 mg/liter, respectively (Table 1). Ceftazidime-avibactam was one dilution more active than ceftazidime alone, based on MIC_{90} values (Table 1).

TABLE 1 *In vitro* activities of ceftazidime-avibactam and comparative agents against baseline *Enterobacteriaceae* and *Pseudomonas aeruginosa* clinical isolates for all randomized patients[a]

Baseline pathogen and agent (no. of pathogens tested)	MIC (mg/liter)		
	Range	MIC_{50}	MIC_{90}
Enterobacteriaceae			
All *Enterobacteriaceae* (803)			
Ceftazidime-avibactam	≤0.008 to >256	0.12	0.25
Ceftazidime	≤0.03 to >64	0.12	32
Amikacin	0.5 to >64	2	4
Aztreonam	≤0.03 to >64	0.06	64
Cefepime	≤0.008 to >16	0.03	>16
Ceftaroline	≤0.008 to >256	0.12	>256
Ceftriaxone	≤0.015 to >32	0.06	>32
Gentamicin	≤0.12 to >16	0.5	>16
Imipenem	0.06 to 16	0.12	0.5
Levofloxacin	0.008 to >8	0.06	>8
Meropenem	0.008 to >8	0.015	0.06
Piperacillin-tazobactam	≤0.06 to >128	2	16
Tigecycline	0.06 to 9	0.25	1
Trimethoprim-sulfamethoxazole	≤0.25 to >8	≤0.25	>8
Citrobacter freundii complex (32)			
Ceftazidime-avibactam	0.03 to 0.5	0.12	0.25
Ceftazidime	0.12 to >64	0.25	2
Amikacin	0.5 to 4	1	2
Aztreonam	≤0.03 to >64	0.12	16
Cefepime	0.015 to >16	0.03	1
Ceftaroline	0.06 to >256	0.12	128
Ceftriaxone	0.03 to >32	0.12	>32
Gentamicin	0.25 to >16	0.5	0.5
Imipenem	0.12 to 1	0.25	0.5
Levofloxacin	0.015 to 8	0.06	0.5
Meropenem	0.008 to 0.06	0.015	0.03
Piperacillin-tazobactam	0.5 to >128	2	128
Tigecycline	0.12 to 2	0.25	0.5
Trimethoprim-sulfamethoxazole	≤0.25 to >8	≤0.25	≤0.25
Enterobacter aerogenes (10)			
Ceftazidime-avibactam	0.12 to 2	0.12	0.5
Ceftazidime	0.12 to >64	0.12	0.5
Amikacin	1 to >64	1	2
Aztreonam	≤0.03 to >64	≤0.03	0.25
Cefepime	0.03 to >16	0.03	0.06
Ceftaroline	0.06 to >256	0.12	0.25
Ceftriaxone	0.06 to >32	0.06	0.25
Gentamicin	0.25 to >16	0.5	0.5
Imipenem	0.12 to 1	0.5	1
Levofloxacin	0.03 to 0.12	0.06	0.12
Meropenem	0.015 to 0.06	0.03	0.03
Piperacillin-tazobactam	1 to >128	4	4
Tigecycline	0.25 to 1	0.5	0.5
Trimethoprim-sulfamethoxazole	≤0.25 to >8	≤0.25	0.5
Enterobacter cloacae (29)			
Ceftazidime-avibactam	0.06 to >256	0.25	2
Ceftazidime	0.06 to >64	0.5	>64
Amikacin	1 to >64	1	8
Aztreonam	≤0.03 to >64	0.12	>64
Cefepime	0.015 to >16	0.06	>16
Ceftaroline	0.03 to >256	0.25	>256
Ceftriaxone	≤0.015 to >32	0.25	>32
Gentamicin	0.25 to >16	0.5	>16
Imipenem	0.12 to 8	0.25	0.5
Levofloxacin	0.03 to >8	0.06	8
Meropenem	0.015 to >8	0.03	0.5
Piperacillin-tazobactam	0.5 to >128	4	>128
Tigecycline	0.5 to 8	0.5	1
Trimethoprim-sulfamethoxazole	≤0.25 to >8	≤0.25	>8

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TABLE 1 (Continued)

Baseline pathogen and agent (no. of pathogens tested)	MIC (mg/liter)		
	Range	MIC_{50}	MIC_{90}
Escherichia coli (549)			
Ceftazidime-avibactam	≤0.008 to 4	0.06	0.12
Ceftazidime	≤0.03 to >64	0.12	8
Amikacin	0.5 to >64	2	4
Aztreonam	≤0.03 to >64	0.06	16
Cefepime	≤0.008 to >16	0.03	16
Ceftaroline	≤0.008 to >256	0.06	>256
Ceftriaxone	≤0.015 to >32	0.06	>32
Gentamicin	0.25 to >16	0.5	>16
Imipenem	0.06 to 0.5	0.12	0.12
Levofloxacin	0.008 to >8	0.03	>8
Meropenem	0.008 to 0.5	0.015	0.03
Piperacillin-tazobactam	≤0.06 to >128	2	8
Tigecycline	0.06 to 2	0.25	0.5
Trimethoprim-sulfamethoxazole	≤0.25 to >8	≤0.25	>8
Klebsiella oxytoca (32)			
Ceftazidime-avibactam	0.03 to 0.25	0.06	0.12
Ceftazidime	≤0.03 to 0.25	0.12	0.12
Amikacin	0.5 to 4	1	1
Aztreonam	≤0.03 to 1	0.06	0.25
Cefepime	0.015 to 0.06	0.03	0.03
Ceftaroline	0.03 to 0.5	0.12	0.25
Ceftriaxone	≤0.015 to 0.12	0.03	0.06
Gentamicin	≤0.12 to 1	0.25	0.5
Imipenem	0.06 to 0.25	0.12	0.25
Levofloxacin	0.03 to 1	0.06	0.06
Meropenem	0.015 to 0.03	0.03	0.03
Piperacillin-tazobactam	0.5 to 4	2	2
Tigecycline	0.25 to 0.5	0.25	0.5
Trimethoprim-sulfamethoxazole	≤0.25 to 0.5	≤0.25	≤0.25
Klebsiella pneumoniae (100)			
Ceftazidime-avibactam	≤0.008 to >256	0.12	0.5
Ceftazidime	≤0.03 to >64	0.12	>64
Amikacin	0.5 to >64	1	2
Aztreonam	≤0.03 to >64	≤0.03	>64
Cefepime	0.015 to >16	0.03	>16
Ceftaroline	0.015 to >256	0.12	>256
Ceftriaxone	≤0.015 to >32	0.06	>32
Gentamicin	≤0.12 to >16	0.25	>16
Imipenem	0.06 to 16	0.12	0.25
Levofloxacin	0.015 to >8	0.06	>8
Meropenem	0.015 to >8	0.03	0.12
Piperacillin-tazobactam	0.5 to >128	2	>128
Tigecycline	0.25 to 4	0.5	2
Trimethoprim-sulfamethoxazole	≤0.25 to >8	≤0.25	>8
Proteus mirabilis (17)			
Ceftazidime-avibactam	0.015 to 2	0.03	0.5
Ceftazidime	≤0.03 to >64	0.06	32
Amikacin	1 to 16	4	8
Aztreonam	≤0.03 to 2	≤0.03	0.5
Cefepime	0.03 to 2	0.06	1
Ceftaroline	0.03 to >256	0.06	256
Ceftriaxone	≤0.015 to >32	≤0.015	>32
Gentamicin	0.5 to >16	1	>16
Imipenem	0.12 to 4	1	4
Levofloxacin	0.03 to >8	0.12	>8
Meropenem	0.03 to 0.12	0.06	0.12
Piperacillin-tazobactam	≤0.06 to 16	0.25	4
Tigecycline	2 to 8	4	4
Trimethoprim-sulfamethoxazole	≤0.25 to >8	≤0.25	>8
Pseudomonas aeruginosa (70)			
Ceftazidime-avibactam	0.5 to 32	2	4
Ceftazidime	1 to >64	2	8

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TABLE 1 (Continued)

Baseline pathogen and agent (no. of pathogens tested)	MIC (mg/liter)		
	Range	MIC_{50}	MIC_{90}
Amikacin	≤0.12 to >64	4	8
Cefepime	0.5 to >16	2	8
Ceftriaxone	4 to >32	32	>32
Gentamicin	≤0.12 to >16	1	2
Imipenem	0.5 to 16	1	2
Levofloxacin	0.03 to >8	0.5	>8
Meropenem	0.03 to >8	0.12	2
Piperacillin-tazobactam	0.5 to >128	4	16

[a]Total of 1,066 randomized patients. Some patients had more than one pathogen isolated. Multiple isolates of the same species from the same patient were counted only once using the isolate with the highest MIC to the study drug received. For bacteremic patients, multiple isolates of the same species from the same patient were counted only once using the isolate with the highest MIC to the study drug received across culture source (intra-abdominal site or blood).

The ceftazidime-avibactam MIC values for other baseline non-*Enterobacteriaceae* Gram-negative pathogens with <10 isolates were as follows: *Aeromonas* spp. ($n = 2$), with an MIC range of 0.12 to 0.25 mg/liter; and other *Pseudomonas* spp. ($n = 6$), with an MIC range of 0.25 to 8 mg/liter.

***In vitro* activity against Gram-positive and anaerobic isolates.** The *in vitro* activities of ceftazidime-avibactam and comparators against Gram-positive baseline isolates are summarized in Table 2. The MIC_{90} values for vancomycin, linezolid, and daptomycin against the Gram-positive isolates characterized in this study were typically ≤2 mg/liter, with *E. faecium* and other enterococci having a daptomycin MIC_{90} of 4 mg/liter (Table 2).

The MIC_{90} values for metronidazole against baseline anaerobe species with ≥10 isolates were 1 to 4 mg/liter, and the MIC_{90} values for meropenem against baseline anaerobes were 0.03 to 4 mg/liter, indicating that both drugs were active against these isolates (Table 3).

***In vitro* activity against ceftazidime-nonsusceptible Gram-negative isolates.** The overall ceftazidime-avibactam MIC_{90} value for 109 ceftazidime-nonsusceptible *Enterobacteriaceae* isolates was 2 mg/liter (Table 4). The MIC frequency distributions for ceftazidime-avibactam and ceftazidime against ceftazidime-nonsusceptible *Enterobacteriaceae* are shown in Fig. 1. Most isolates tested at ≤4 mg/liter for ceftazidime-avibactam, and there was a left shift in MIC distribution versus ceftazidime alone. Four (3.7%) of the 109 ceftazidime-nonsusceptible isolates were also found to be nonsusceptible to ceftazidime-avibactam (Fig. 1). These isolates (two *Enterobacter cloacae* from India and two *K. pneumoniae* isolates, with one from Romania and one from India) had previously been determined to express the NDM-1 or NDM-4 metallo-β-lactamase (11).

The most common ceftazidime-nonsusceptible isolates were *E. coli* (59/109 [54.1%] isolates; ceftazidime-avibactam MIC_{50}, 0.12 mg/liter; MIC_{90}, 2 mg/liter), *K. pneumoniae* (27/109 [24.8%] isolates; ceftazidime-avibactam MIC_{50}, 0.5 mg/liter; MIC_{90}, 2 mg/liter), and *Enterobacter cloacae* (10/109 [9.2%] isolates; ceftazidime-avibactam MIC_{50}, 1 mg/liter; MIC_{90}, >256 mg/liter).

The ceftazidime-avibactam MIC values for six ceftazidime-nonsusceptible *P. aeruginosa* isolates ranged from 8 to 32 mg/liter (Table 4). There was a trend for a left shift in the MIC distribution for ceftazidime-avibactam versus ceftazidime alone in these ceftazidime-nonsusceptible isolates, with two (33.3%) of the six ceftazidime-nonsusceptible isolates being brought into the susceptible range when ceftazidime was combined with avibactam. For these ceftazidime-nonsusceptible *P. aeruginosa* isolates, the MICs of meropenem and imipenem ranged from 2 to >8 mg/liter and 1 to 16 mg/liter, respectively.

Overall, 85 *Enterobacteriaceae* isolates (61 *E. coli* and 24 *K. pneumoniae*) were phenotypically positive for an ESBL (Table 5). Ceftazidime-avibactam MIC_{90} values against ESBL-positive *E. coli* and *K. pneumoniae* isolates were 0.25 mg/liter and 1 mg/liter, respectively. The respective MIC_{90} values against ESBL-negative *E. coli* and *K. pneumoniae* isolates were 0.12 mg/liter.

TABLE 2 *In vitro* activities of ceftazidime-avibactam and comparative agents against baseline Gram-positive isolates for all randomized patients[a]

Baseline pathogen and agent (no. of tested pathogens)	MIC (mg/liter)		
	Range	MIC_{50}	MIC_{90}
Enterococcus faecalis (59)			
Ceftazidime-avibactam	32 to >256	>256	>256
Ceftazidime	32 to >64	>64	>64
Ceftaroline	0.25 to 256	1	64
Clindamycin	4 to >16	>16	>16
Daptomycin	0.06 to 4	1	2
Levofloxacin	0.5 to >8	1	>8
Linezolid	1 to 2	2	2
Meropenem	1 to >8	4	>8
Teicoplanin	0.25 to 2	0.5	1
Ticarcillin-clavulanate	32 to >128	64	>128
Tigecycline	0.06 to 0.25	0.12	0.12
Trimethoprim-sulfamethoxazole	≤0.25 to >8	≤0.25	>8
Vancomycin	0.5 to 2	1	2
Enterococcus faecium (39)			
Ceftazidime-avibactam	32 to >256	>256	>256
Ceftazidime	16 to >64	>64	>64
Ceftaroline	0.12 >256	0.5	>256
Clindamycin	0.06 to >16	8	>16
Daptomycin	0.5 to 8	4	4
Levofloxacin	0.5 to >8	2	>8
Linezolid	1 to 4	2	2
Meropenem	0.25 to >8	>8	>8
Teicoplanin	0.25 to >32	1	1
Tigecycline	0.03 to 0.12	0.06	0.12
Trimethoprim-sulfamethoxazole	≤0.25 to >8	≤0.25	>8
Vancomycin	0.25 to >32	0.5	1
Other *Enterococcus* spp. (37)[b]			
Ceftazidime-avibactam	1 to >256	128	>256
Ceftazidime	2 to >64	>64	>64
Ceftaroline	≤0.008 to 4	0.25	1
Clindamycin	0.5 to >16	4	>16
Daptomycin	0.12 to 4	0.5	4
Levofloxacin	0.25 to >8	1	2
Linezolid	1 to 4	2	2
Meropenem	0.03 to >8	4	8
Teicoplanin	≤0.12 to 2	0.5	1
Tigecycline	≤0.015 to 0.12	0.03	0.06
Trimethoprim-sulfamethoxazole	≤0.25 to >8	≤0.25	≤0.25
Vancomycin	0.25 to 8	0.5	2
Streptococcus anginosus group (131)[c]			
Ceftazidime-avibactam	≤0.06 to >4	4	>4
Ceftazidime	0.5 to >4	4	>4
Clindamycin	≤0.015 to >1	0.03	0.06
Daptomycin	0.06 to 1	0.5	1
Levofloxacin	≤0.12 to 1	0.5	1
Linezolid	≤0.12 to 2	2	2
Meropenem	≤0.015 to 0.25	0.06	0.12
Tigecycline	≤0.008 to 0.25	≤0.008	0.03
Trimethoprim-sulfamethoxazole	≤0.06 to 0.5	≤0.06	≤0.06
Vancomycin	0.5 to 1	0.5	1
Other streptococci (46)[d]			
Ceftazidime-avibactam	0.12 to >4	1	>4
Ceftazidime	0.12 to >4	1	>4
Clindamycin	≤0.015 to >1	0.03	0.06
Daptomycin	≤0.03 to 1	0.5	1
Levofloxacin	0.5 to 4	1	2
Linezolid	0.5 to 2	1	2
Meropenem	≤0.015 to 0.5	0.03	0.25
Tigecycline	≤0.008 to 0.5	0.06	0.25

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TABLE 2 (Continued)

Baseline pathogen and agent (no. of tested pathogens)	MIC (mg/liter)		
	Range	MIC_{50}	MIC_{90}
Trimethoprim-sulfamethoxazole	≤0.06 to 2	0.12	1
Vancomycin	0.25 to 1	0.5	0.5
Staphylococcus aureus (33)			
Ceftazidime-avibactam	4 to >256	8	128
Ceftazidime	4 to >64	8	64
Ceftaroline	0.12 to 32	0.25	1
Clindamycin	0.12 to >16	0.12	>16
Daptomycin	0.25 to 0.5	0.5	0.5
Levofloxacin	0.06 to >8	0.25	4
Linezolid	1 to 4	2	2
Meropenem	0.03 to >8	0.06	2
Teicoplanin	0.5 to 4	1	1
Tigecycline	0.06 to 1	0.12	0.25
Trimethoprim-sulfamethoxazole	≤0.25 to ≤0.25	≤0.25	≤0.25
Vancomycin	0.5 to 1	0.5	1

[a]Total of 1,066 randomized patients. Data are provided for pathogens identified in at least 10 patients. A patient could have more than one pathogen isolated. Multiple isolates of the same species from the same patient were counted only once using the isolate with the highest MIC to the study drug received. For bacteremic patients, multiple isolates of the same species from the same patient were counted only once using the isolate with the highest MIC to the study drug received across culture source (intra-abdominal site or blood).

[b]Other *Enterococcus* spp. include *Enterococcus avium* ($n = 23$), *Enterococcus casseliflavus* ($n = 3$), *Enterococcus durans* ($n = 1$), *Enterococcus gallinarum* ($n = 3$), *Enterococcus hirae* ($n = 3$), *Enterococcus raffinosus* ($n = 1$), and *Enterococcus thailandicus* ($n = 3$).

[c]*Streptococcus anginosus* group includes *Streptococcus anginosus* group ($n = 130$) and *Streptococcus constellatus* ($n = 1$).

[d]Other streptococci include *Streptococcus bovis* group ($n = 10$), *Streptococcus dysgalactiae* ($n = 3$), *Streptococcus mitis* group ($n = 26$), *Streptococcus pyogenes* ($n = 2$), and *Streptococcus salivarius* group ($n = 5$).

DISCUSSION

The *in vitro* activities of ceftazidime-avibactam and comparators against 1,440 clinical isolates obtained from intra-abdominal and blood cultures from all randomized patients ($n = 1,066$) with cIAI enrolled in a phase 3 clinical trial (ClinicalTrials.gov identifier NCT01499290) (10) were evaluated in this study. Overall, based on the modified-intention-to-treat (MITT) population (which may reflect fewer patients and isolates than the all-randomized-patient set and comprised 1,043 patients who met the disease definition of cIAI and received any amount of study drug), 414 patients (39.7%) in this study had monomicrobial infections, and 417 patients (40.0%) had polymicrobial infections, with the remainder having no study-qualifying pathogen identified (10). In addition, bacteremia was identified in 36 patients (3.5%) (10). These findings are similar to those of another phase 3 ceftazidime-avibactam trial in adult patients with cIAI enrolled in Asian countries, where 42.9%, 25.5%, and 3.5% of patients were found to have monomicrobial infections, polymicrobial infections, and bacteremia, respectively (12).

Gram-negative species were found to predominate in this study, with 56% of the isolates being members of the *Enterobacteriaceae* family, 5% being *P. aeruginosa*, 21% being Gram-positive aerobes, and 18% being anaerobic species. These findings are similar to those of recent surveillance studies (13), other recent phase 3 studies in adult patients with cIAIs (12, 14), and the Complicated Intra-Abdominal Infections Worldwide Observational (CIAOW) study (15). The CIAOW study included 1,898 patients from 68 medical centers worldwide between October 2012 and March 2013 and identified *Enterobacteriaceae* (most commonly *E. coli* and *K. pneumoniae*) as the major pathogens involved in cIAI (15). Thus, the pathogens isolated in the ceftazidime-avibactam phase 3 cIAI study described here are representative of those seen in clinical practice (8, 13, 15, 16, 17, 18), and the current study provides further confirmation of the association between *Enterobacteriaceae* and cIAIs (10).

In this study, ceftazidime-avibactam was found to be highly active *in vitro* against

TABLE 3 *In vitro* activities of ceftazidime-avibactam and comparative agents against anaerobic species isolated at baseline for all randomized patients[a]

Baseline pathogen and agent (no. of pathogens tested)	MIC (mg/liter)		
	Range	MIC_{50}	MIC_{90}
Bacteroides fragilis group (96)			
Ceftazidime-avibactam	1 to 32	4	8
Ceftazidime	4 to >128	32	>128
Amoxicillin-clavulanate	0.25 to 16	0.5	4
Ampicillin	1 to >128	32	>128
Clindamycin	≤0.015 to >32	1	>32
Meropenem	0.06 to 8	0.12	4
Metronidazole	0.25 to 8	1	2
Other *Bacteroides fragilis* group (163)[b]			
Ceftazidime-avibactam	2 to >128	64	128
Ceftazidime	8 to >128	>128	>128
Amoxicillin-clavulanate	0.25 to >128	1	8
Ampicillin	1 to >128	32	>128
Clindamycin	0.03 to >32	8	>32
Meropenem	0.06 to 2	0.25	1
Metronidazole	0.25 to 8	2	4
Other *Bacteroides* spp. (21)[c]			
Ceftazidime-avibactam	≤0.06 to 64	16	64
Ceftazidime	0.12 to >128	32	>128
Amoxicillin-clavulanate	≤0.06 to 8	0.5	2
Ampicillin	≤0.06 to >128	16	>128
Clindamycin	≤0.015 to >32	2	>32
Meropenem	≤0.015 to 2	0.25	1
Metronidazole	0.12 to 8	1	2
Clostridium perfringens (14)			
Ceftazidime-avibactam	≤0.06 to ≤0.06	≤0.06	≤0.06
Ceftazidime	0.25 to 8	1	4
Amoxicillin-clavulanate	≤0.06 to 0.12	≤0.06	≤0.06
Ampicillin	≤0.06 to 0.25	≤0.06	0.12
Clindamycin	0.03 to >32	1	4
Meropenem	≤0.015 to 0.25	≤0.015	0.03
Metronidazole	0.25 to 4	1	4
Other *Clostridium* spp. (28)[d]			
Ceftazidime-avibactam	≤0.06 to >128	16	>128
Ceftazidime	2 to >128	32	>128
Amoxicillin-clavulanate	≤0.06 to 2	0.5	1
Ampicillin	≤0.06 to 64	0.5	8
Clindamycin	0.06 to >32	1	>32
Meropenem	≤0.015 to 4	1	4
Metronidazole	≤0.06 to 4	0.5	2
Eggerthella lenta (13)			
Ceftazidime-avibactam	>128 to >128	>128	>128
Ceftazidime	>128 to >128	>128	>128
Amoxicillin-clavulanate	0.25 to 2	1	1
Ampicillin	1 to 4	2	2
Clindamycin	0.06 to >32	0.5	>32
Meropenem	0.25 to 1	0.25	0.5
Metronidazole	0.5 to 16	2	4
Parvimonas micra (16)			
Ceftazidime-avibactam	≤0.06 to 4	≤0.06	0.5
Ceftazidime	0.12 to 8	0.5	2
Amoxicillin-clavulanate	≤0.06 to 0.5	≤0.06	0.25
Ampicillin	≤0.06 to 8	≤0.06	0.25
Clindamycin	0.06 to 4	0.25	0.5
Meropenem	≤0.015 to 0.25	0.03	0.12
Metronidazole	0.12 to 1	0.5	1

(Continued on next page)

TABLE 3 (Continued)

Baseline pathogen and agent (no. of pathogens tested)	MIC (mg/liter)		
	Range	MIC_{50}	MIC_{90}
Prevotella spp. (21)[e]			
Ceftazidime-avibactam	≤0.06 to 8	0.5	4
Ceftazidime	0.12 to 128	2	16
Amoxicillin-clavulanate	≤0.06 to 1	0.12	0.5
Ampicillin	≤0.06 to 16	0.25	8
Clindamycin	≤0.015 to >32	≤0.015	>32
Meropenem	≤0.015 to 0.25	0.03	0.12
Metronidazole	0.12 to 8	1	4

[a]Total of 1,066 randomized patients. Data are provided for pathogens identified in at least 10 patients.
[b]Other *Bacteroides fragilis* group includes *Bacteroides caccae* (*n* = 3), *Bacteroides ovatus* (*n* = 41), *Bacteroides stercoris* (*n* = 11), *Bacteroides thetaiotaomicron* (*n* = 47), *Bacteroides uniformis* (*n* = 15), *Bacteroides vulgatus* (*n* = 16), *Parabacteroides distasonis* (*n* = 29), and *Parabacteroides merdae* (*n* = 1).
[c]Other *Bacteroides* spp. includes *Bacteroides* (*n* = 5), *Bacteroides dorei* (*n* = 4), *Bacteroides faecis* (*n* = 4), *Bacteroides nordii* (*n* = 3), *Bacteroides salyersiae* (*n* = 1), *Bacteroides splanchnicus* (*n* = 3), and *Bacteroides xylanisolvens* (*n* = 1).
[d]Other *Clostridium* spp. includes *Clostridium aldenense* (*n* = 1), *Clostridium bolteae* (*n* = 1), *Clostridium citroniae* (*n* = 1), *Clostridium clostridioforme* (*n* = 3), *Clostridium hathewayi* (*n* = 3), *Clostridium innocuum* (*n* = 9), *Clostridium ramosum* (*n* = 6), *Clostridium septicum* (*n* = 1), *Clostridium sporogenes* (*n* = 1), and *Clostridium symbiosum* (*n* = 2).
[e]*Prevotella* spp. includes *Prevotella* (*n* = 1), *Prevotella bivia* (*n* = 2), *Prevotella buccae* (*n* = 6), *Prevotella denticola* (*n* = 2), *Prevotella heparinolytica* (1), *Prevotella intermedia* (*n* = 4), *Prevotella melaninogenica* (*n* = 2), *Prevotella nigrescens* (2), and *Prevotella oralis* (*n* = 1).

baseline *Enterobacteriaceae* isolates, with an overall MIC_{90} of 0.25 mg/liter (128-fold lower than that of ceftazidime alone) and an MIC_{90} of ≤2 mg/liter against each of the individual members of the *Enterobacteriaceae* family. These results are in agreement with the clinical results of the phase 3 study, which showed that ceftazidime-avibactam plus metronidazole is effective in patients with cIAI, with a clinical cure rate similar to that for meropenem in patients with Gram-negative infection (10). In addition, no significant trends in clinical outcomes were observed between groups of patients subdivided according to patient or disease baseline characteristics, including mono- versus polymicrobial infection and the presence of bacteremia (10).

The *in vitro* activity of ceftazidime-avibactam against clinical *Enterobacteriaceae* isolates has also been investigated in another phase 3 study (ClinicalTrials.gov identifiers NCT01599806 and NCT01595438) (19), which evaluated the efficacy and safety of ceftazidime-avibactam versus doripenem in patients with complicated urinary tract infections (cUTIs). Although the *in vitro* results of the phase 3 cIAI study presented here and the phase 3 cUTI study cannot be directly compared because of differences in the patient populations, study centers, and countries included, the MIC_{90} values of 0.25 mg/liter and 1 mg/liter against *E. coli* and *K. pneumoniae*, respectively, in the cUTI study were not that dissimilar from those observed in the current cIAI study (0.12 mg/liter and 0.5 mg/liter, respectively) (19).

A similar trend was seen in the *in vitro* results from the phase 3 cUTI study against *P. aeruginosa* isolates; the MIC_{90} for ceftazidime-avibactam in the cUTI study was 8 mg/liter and was 32 mg/liter for ceftazidime alone (the MIC_{90} for ceftazidime-avibactam in the current cIAI study was 4 mg/liter and was 8 mg/liter for ceftazidime alone) (19). The results of recent surveillance studies performed in the United States (13) also confirmed the increased susceptibility of *P. aeruginosa* isolates to ceftazidime-avibactam compared with ceftazidime alone. In this recent surveillance study, which included Gram-negative isolates collected from abdominal infection sites between 2012 and 2014 in U.S. hospitals, the MIC_{90} for ceftazidime-avibactam against *P. aeruginosa* was also found to be 4 mg/liter (13), and the MIC_{90} for ceftazidime alone was 32 mg/liter (13).

The majority of the 109 ceftazidime-nonsusceptible Gram-negative isolates in the current study tested with a ceftazidime-avibactam MIC of ≤2 mg/liter, with only four isolates not susceptible to ceftazidime-avibactam (Fig. 1). These findings are in line with the *in vitro* data from the phase 3 cUTI study and also an open-label study (ClinicalTrials.gov

TABLE 4 *In vitro* activity of ceftazidime-avibactam and comparative agents against ceftazidime-nonsusceptible Gram-negative isolates for all randomized patients[a]

Baseline pathogen and agent (no. of pathogens tested)	MIC (mg/liter)		
	Range	MIC_{50}	MIC_{90}
All *Enterobacteriaceae* (109)			
Ceftazidime-avibactam	≤0.008 to >256	0.25	2
Ceftazidime	8 to >64	32	>64
Amikacin	0.5 to >64	4	>64
Aztreonam	0.12 to >64	64	>64
Cefepime	0.06 to >16	>16	>16
Ceftaroline	0.25 to >256	>256	>256
Ceftriaxone	1 to >32	>32	>32
Gentamicin	≤0.12 to >16	>16	>16
Imipenem	0.06 to 16	0.12	2
Levofloxacin	0.03 to >8	>8	>8
Meropenem	0.015 to >8	0.03	0.5
Piperacillin-tazobactam	0.25 to >128	16	>128
Tigecycline	0.12 to 8	0.5	2
Trimethoprim-sulfamethoxazole	≤0.25 to >8	>8	>8
Enterobacter cloacae (10)			
Ceftazidime-avibactam	0.25 to >256	1	>256
Ceftazidime	16 to >64	>64	>64
Amikacin	2 to >64	4	16
Aztreonam	8 to >64	>64	>64
Cefepime	2 to >16	>16	>16
Ceftaroline	32 to >256	>256	>256
Ceftriaxone	32 to >32	>32	>32
Gentamicin	0.25 to >16	>16	>16
Imipenem	0.25 to 8	0.5	8
Levofloxacin	0.5 to >8	8	>8
Meropenem	0.03 to >8	0.06	8
Piperacillin-tazobactam	4 to >128	64	>128
Tigecycline	0.5 to 8	0.5	4
Trimethoprim-sulfamethoxazole	≤0.25 to >8	>8	>8
Escherichia coli (59)			
Ceftazidime-avibactam	≤0.008 to 4	0.12	2
Ceftazidime	8 to >64	32	>64
Amikacin	0.5 to >64	4	8
Aztreonam	8 to >64	64	>64
Cefepime	0.06 to >16	>16	>16
Ceftaroline	0.25 to >256	>256	>256
Ceftriaxone	1 to >32	>32	>32
Gentamicin	0.25 to >16	2	>16
Imipenem	0.06 to 0.5	0.12	0.25
Levofloxacin	0.03 to >8	>8	>8
Meropenem	0.015 to 0.5	0.015	0.03
Piperacillin-tazobactam	1 to >128	8	>128
Tigecycline	0.12 to 1	0.25	0.5
Trimethoprim-sulfamethoxazole	≤0.25 to >8	>8	>8
Klebsiella pneumoniae (27)			
Ceftazidime-avibactam	0.12 to >256	0.5	2
Ceftazidime	8 to >64	>64	>64
Amikacin	0.5 to >64	2	>64
Aztreonam	2 to >64	>64	>64
Cefepime	0.25 to >16	>16	>16
Ceftaroline	8 to >256	>256	>256
Ceftriaxone	8 to >32	>32	>32
Gentamicin	≤0.12 to >16	>16	>16
Imipenem	0.12 to 16	0.12	8
Levofloxacin	0.06 to >8	>8	>8
Meropenem	0.015 to >8	0.03	8
Piperacillin-tazobactam	4 to >128	128	>128
Tigecycline	0.5 to 4	1	4
Trimethoprim-sulfamethoxazole	≤0.25 to >8	>8	>8

(Continued on next page)

TABLE 4 (Continued)

Baseline pathogen and agent (no. of pathogens tested)	MIC (mg/liter)		
	Range	MIC_{50}	MIC_{90}
Pseudomonas aeruginosa (6)			
Ceftazidime-avibactam	8 to 32	NA	NA
Ceftazidime	32 to >64	NA	NA
Amikacin	8 to >64	NA	NA
Cefepime	16 to >16	NA	NA
Ceftriaxone	>32 to >32	NA	NA
Ciprofloxacin	>4 to >4	NA	NA
Gentamicin	2 to >16	NA	NA
Imipenem	1 to 16	NA	NA
Levofloxacin	>8 to >8	NA	NA
Meropenem	2 to >8	NA	NA
Piperacillin-tazobactam	32 to >128	NA	NA

[a]Total of 1,066 randomized patients. NA, not applicable (MIC_{50} and MIC_{90} were not calculated for pathogens identified in <10 patients). Data are provided for pathogens identified in at least 10 patients, with the exception of *Pseudomonas aeruginosa*, $n = 6$; ceftazidime-avibactam MIC values for other pathogens are as follows: *Citrobacter freundii* complex ($n = 3$), MIC range, 0.25 to 0.5 mg/liter; *Enterobacter aerogenes* ($n = 1$), MIC, 2 mg/liter, *Proteus mirabilis* ($n = 5$), MIC range, 0.015 to 2 mg/liter; other *Enterobacteriaceae* ($n = 4$), MIC range, 0.03 to 0.12 mg/liter; *Alcaligenes faecalis* ($n = 3$), MIC range, 4 to 4 mg/liter; and *Comamonas testosteroni* ($n = 1$), MIC, >256 mg/liter. A patient could have more than one pathogen isolated. Multiple isolates of the same species from the same patient were counted only once using the isolate with the highest MIC to the study drug received. For bacteremic patients, multiple isolates of the same species from the same patient were counted only once using the isolate with the highest MIC to the study drug received across culture source (intra-abdominal site or blood).

identifier NCT01644643) evaluating the efficacy and safety of ceftazidime-avibactam versus the best available therapy in patients with ceftazidime-resistant cIAI and cUTI; both of these studies indicated that the addition of avibactam to ceftazidime restores the *in vitro* activity of ceftazidime against ceftazidime-nonsusceptible *Enterobacteriaceae* (MIC_{90}, 1 mg/liter in both studies) (19, 20).

The CIAOW study data identified ESBL-producing bacteria as the most common drug-resistant pathogens associated with cIAI, comprising 13.7% of all intraoperatively obtained *E. coli* isolates and 18.6% of *K. pneumoniae* isolates (15). Similar to these results, 10.6% of the *Enterobacteriaceae* isolates identified in the current study were confirmed as being phenotypically positive for an ESBL, including 11.1% of the *E. coli* isolates and 24.0% of the *K. pneumoniae* isolates. Also confirming the presence of

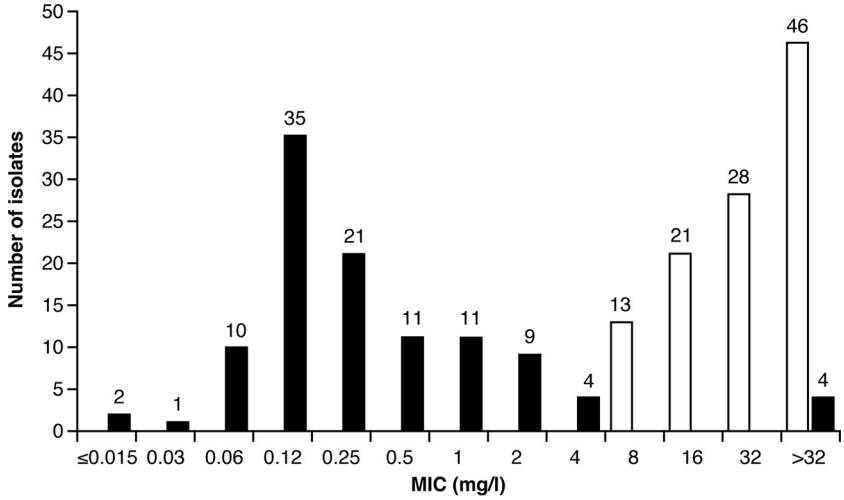

FIG 1 Activities of ceftazidime-avibactam (black bars) and ceftazidime (white bars) against 108 ceftazidime-nonsusceptible *Enterobacteriaceae* (determined for the microbiologically modified intent-to-treat [mMITT] patient analysis set). For *Enterobacteriaceae*, ceftazidime-nonsusceptible isolates were defined as those having a ceftazidime MIC of ≥8 mg/liter. mMITT includes 108 of the 109 ceftazidime-nonsusceptible *Enterobacteriaceae* isolates obtained from all randomized patients.

TABLE 5 *In vitro* activities of ceftazidime-avibactam against *Escherichia coli* and *Klebsiella pneumoniae* baseline isolates by the presence or absence of extended-spectrum β-lactamases for all randomized patients[a]

ESBL status by baseline pathogen (no. of pathogens tested)	MIC (mg/liter)		
	Range	MIC_{50}	MIC_{90}
Escherichia coli			
ESBL positive (61)	≤0.008 to 0.5	0.12	0.25
ESBL negative (487)	≤0.008 to 4	0.06	0.12
Klebsiella pneumoniae			
ESBL positive (24)	0.12 to 2	0.25	1
ESBL negative (76)	≤0.008 to >256	0.12	0.12

[a]Total of 1,066 randomized patients. ESBL, extended-spectrum β-lactamase; NA, not applicable. ESBL status was determined by phenotype based on CLSI confirmatory tests. Some patients had more than one pathogen isolated. Multiple isolates of the same species from the same patient were counted only once using the isolate with the highest MIC to the study drug received. For bacteremic patients, multiple isolates of the same species from the same patient were counted only once using the isolate with the highest MIC to the study drug received across culture source (intra-abdominal site or blood).

ESBL-producing pathogens in patients with cIAI, 7.2% of *Enterobacteriaceae* isolates from cIAI patients in the phase 3 ceftolozane-tazobactam clinical trial tested positive for an ESBL-producing pathogen (14). Of note, the CIAOW study highlighted a difference in the proportion of ESBL-producing pathogens in patients with health care-associated and community-acquired cIAIs, with 20.6% of *E. coli* and 42.8% of *K. pneumoniae* isolates from patients with health care-associated infection confirmed to be ESBL positive. Any variations in the overall proportions of ESBL-producing pathogens identified between these studies could be due to differences in the geographical area included, patient population, hospital epidemiology, and study timing (14, 15).

Previous molecular characterization of Gram-negative isolates in the current cIAI study that met MIC screening criteria for potential ESBLs identified CTX-M variants alone (29.7% [41/138]) or in combination with OXA-1/30 (35.5% [49/138]) as the most commonly carried β-lactamases (11). The prevalence and type of ESBLs among isolates of *Enterobacteriaceae* from this study are representative of the global distribution of ESBLs (21).

Molecular characterization determined that the four ceftazidime-nonsusceptible *Enterobacteriaceae* isolates (two *E. cloacae* and two *K. pneumoniae*) identified in the cIAI study were New Delhi metallo-β-lactamase-producing isolates with a ceftazidime-avibactam MIC of >256 mg/liter (11). Avibactam does not inhibit Ambler class B metallo-β-lactamases, and this is likely to be the cause of the observed nonsusceptibility of these isolates (2, 3, 22). The molecular analysis also identified that the six ceftazidime-nonsusceptible isolates of *P. aeruginosa* in the current cIAI study demonstrated overexpression of chromosomal AmpC alone or in combination with bla_{OXA-10} or bla_{PER-1} (11). It is possible that these isolates may also exhibit other unidentified resistance mechanisms, such as decreased permeability to antimicrobial agents, but all affected patients (two patients in the ceftazidime-avibactam group and four patients in the meropenem group) reached a clinical cure in the study (10). Reassuringly, the clinical cure rates in the ceftazidime-avibactam group as a whole were shown to be similar irrespective of ESBL status (clinical cure rate of 82.2% in patients in whom pathogens did not meet the screening criteria for ESBLs versus 87.5% in patients meeting the MIC screening criteria) (11).

Similar to the CIAOW study (15), the most common Gram-positive and anaerobic pathogens identified in the current cIAI study were in the *Streptococcus* and *Bacteroides* species categories, respectively. Vancomycin, linezolid, and daptomycin were permitted per protocol in the study to treat suspected or confirmed *Enterococcus* or methicillin-resistant *Staphylococcus aureus* (MRSA) infection. The MIC_{90} values for these drugs were within the range of susceptibility to provide coverage against the Gram-positive pathogens isolated. Furthermore, the metronidazole and meropenem MIC_{90} values were also within the range of susceptibility for the anaerobic pathogens isolated.

In conclusion, ceftazidime-avibactam was highly active *in vitro* against isolates of *Enterobacteriaceae* and *P. aeruginosa* obtained from clinical specimens from patients in the phase 3 cIAI clinical trial. These included ESBL-producing *Enterobacteriaceae* isolates and those that were nonsusceptible to ceftazidime.

MATERIALS AND METHODS

The clinical isolates for this study were obtained from two double-dummy double-blind randomized controlled trials that were subsequently combined and analyzed as one study (ClinicalTrials.gov identifier NCT01499290) to assess the efficacy, safety, and tolerability of ceftazidime-avibactam plus metronidazole versus meropenem in adult patients hospitalized with cIAI (10). In addition to the assigned study therapy, in the case of suspected or confirmed concomitant infection with *Enterococcus* or methicillin-resistant *Staphylococcus aureus* (MRSA), patients in either group received open-label vancomycin, linezolid, or daptomycin at the discretion of the investigator (10). Overall, 1,066 patients from 136 study sites in 30 countries in Asia, Europe, North and South America, and South Africa were included between March 2012 and April 2014. Detailed descriptions of the methods for the clinical study and patient demographics have been published previously (10).

Abdominal and blood culture specimens isolated from all randomized patients ($n = 1{,}066$) were processed at the study sites' (or regional) laboratories according to local practices and culture methods. Bacterial isolates from the patient specimens were submitted to a central laboratory (Covance CLS, Indianapolis, IN, USA) for identification and susceptibility testing by broth microdilution, according to Clinical and Laboratory Standards Institute (CLSI) methods (23, 24).

In vitro activity was assessed for ceftazidime-avibactam and various reference antibiotics, including the comparator in the phase 3 trial, meropenem, and representative agents in relevant classes. All agents were tested by reference broth microdilution methods using frozen panels according to the manufacturer's recommendations (Trek Diagnostics, Westlake, OH, USA). For susceptibility testing of ceftazidime-avibactam, avibactam was tested at a constant concentration of 4 mg/liter in doubling dilutions of ceftazidime. CLSI interpretive criteria were used for all isolates, except tigecycline, for which FDA interpretative criteria were used (25). At the time of the cIAI trials, breakpoints for ceftazidime-avibactam had not been approved, but the presumptive interpretive criteria used in the analyses have since been confirmed (9). Ceftazidime-nonsusceptible *Enterobacteriaceae* and *P. aeruginosa* isolates were defined as those testing with ceftazidime MICs of $\geq$8 mg/liter and $\geq$16 mg/liter, respectively.

If there was more than one isolate of a given species in an individual patient at baseline, the strain that tested with the highest MIC to the received study drug was used for the analysis. Phenotypic detection of ESBL production is limited to a few species and was performed according to CLSI guidelines using MIC screening and confirmatory tests (24).

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The ultimate responsibility for opinions, conclusions, and data interpretation lies with the authors.

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G.G.S., P.A.B., and P.N. were employees of and shareholders in AstraZeneca at the time of the study. G.G.S. is currently an employee of Pfizer.

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